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(71) Applicants *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI, S.P.A.** [IT/IT]; VIA PONTINA KM. 30.600, I-00040 POMEZIA (IT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **EMINI, Emilio, A.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **KASLOW, David, C.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **BETT, Andrew, J.** [CA/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **SHIVER, John, W.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **NICOSIA, Alfredo** [IT/IT]; Via Pontina KM. 30.600, I-00040 Pomezia (IT). **LAHM, Armin** [DE/IT]; Via Pontina KM. 30.600, I-00040 Pomezia (IT). **LUZZAGO, Alessandra** [IT/IT]; Via Pontina KM. 30.600, I-00040 Pomezia (IT). **CORTESE, Riccardo** [IT/IT]; Via Pontina KM. 30.600, I-00040 Pomezia (IT). **COLLOCA, Stefano** [IT/IT]; Via Pontina KM. 30.600, I-00040 Pomezia (IT).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

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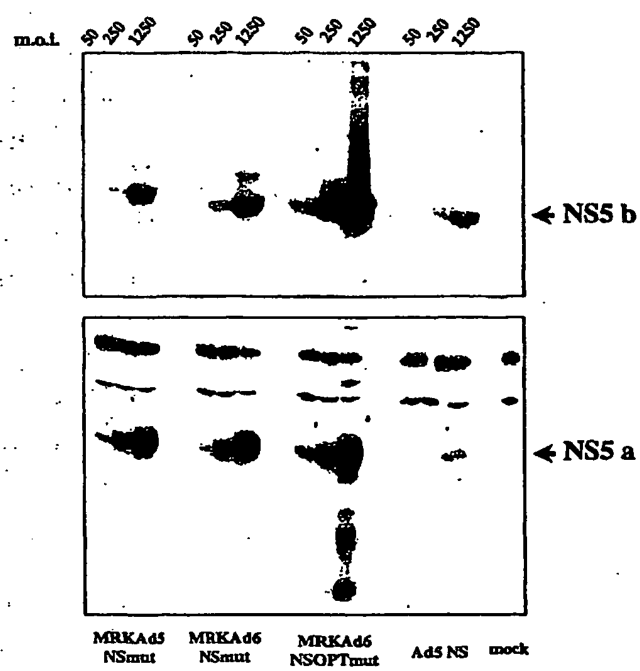
(54) Title: HEPATITIS C VIRUS VACCINE



Western blot on whole-cell extracts from HeLa cells infected at different multiplicity of infection (m.o.i.; indicated at the top) with Adenovectors expressing the different HCV NS cassettes. Mature NS5B and NS5A products were detected with specific antibodies.

(57) Abstract: The present invention features Ad6 vectors and a nucleic acid encoding a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide containing an inactive NS5B RNA-dependent RNA polymerase region. The nucleic acid is particularly useful as a component of an adenovector or DNA plasmid vaccine providing a broad range of antigens for generating an HCV specific cell mediated immune (CMI) response against HCV.

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TITLE OF THE INVENTION
HEPATITIS C VIRUS VACCINE

RELATED APPLICATIONS

The present application claims priority to provisional applications U.S. Serial No. 60/363,774, filed March 13, 2002, and U.S. Serial No. 60/328,655, filed October 11, 2001, each of which are hereby incorporated by reference herein.

BACKGROUND OF THE INVENTION

The references cited in the present application are not admitted to be prior art to the claimed invention.

About 3% of the world's population are infected with the Hepatitis C virus (HCV). (Wasley *et al.*, *Semin. Liver Dis. 20*, 1-16, 2000.) Exposure to HCV results in an overt acute disease in a small percentage of cases, while in most instances the virus establishes a chronic infection causing liver inflammation and slowly progresses into liver failure and cirrhosis. (Iwarson, *FEMS Microbiol. Rev. 14*, 201-204, 1994.) In addition, epidemiological surveys indicate an important role of HCV in the pathogenesis of hepatocellular carcinoma. (Kew, *FEMS Microbiol. Rev. 14*, 211-220, 1994, Alter, *Blood 85*, 1681-1695, 1995.)

Prior to the implementation of routine blood screening for HCV in 1992, most infections were contracted by inadvertent exposure to contaminated blood, blood products or transplanted organs. In those areas where blood screening of HCV is carried out, HCV is primarily contracted through direct percutaneous exposure to infected blood, *i.e.*, intravenous drug use. Less frequent methods of transmission include perinatal exposure, hemodialysis, and sexual contact with an HCV infected person. (Alter *et al.*, *N. Engl. J. Med. 341(8)*, 556-562, 1999, Alter, *J. Hepatol. 31 Suppl.* 88-91, 1999. *Semin. Liver. Dis. 201*, 1-16, 2000.)

The HCV genome consists of a single strand RNA about 9.5 kb encoding a precursor polyprotein of about 3000 amino acids. (Choo *et al.*, *Science 244*, 362-364, 1989, Choo *et al.*, *Science 244*, 359-362, 1989, Takamizawa *et al.*, *J. Virol. 65*, 1105-1113, 1991.) The HCV polyprotein contains the viral proteins in the order: C-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-NS5B.

Individual viral proteins are produced by proteolysis of the HCV polyprotein. Host cell proteases release the putative structural proteins C, E1, E2, and

p7, and create the N-terminus of NS2 at amino acid 810. (Mizushima *et al.*, *J. Virol.* *68*, 2731-2734, 1994, Hijikata *et al.*, *P.N.A.S. USA* *90*, 10773-10777, 1993.)

The non-structural proteins NS3, NS4A, NS4B, NS5A and NS5B presumably form the virus replication machinery and are released from the polyprotein. A zinc-dependent protease associated with NS2 and the N-terminus of NS3 is responsible for cleavage between NS2 and NS3. (Grakoui *et al.*, *J. Virol.* *67*, 1385-1395, 1993, Hijikata *et al.*, *P.N.A.S. USA* *90*, 10773-10777, 1993.) A distinct serine protease located in the N-terminal domain of NS3 is responsible for proteolytic cleavages at the NS3/NS4A, NS4A/NS4B, NS4B/NS5A and NS5A/NS5B junctions. (Bartenschlager *et al.*, *J. Virol.* *67*, 3835-3844, 1993, Grakoui *et al.*, *Proc. Natl. Acad. Sci. USA* *90*, 10583-10587, 1993, Tomei *et al.*, *J. Virol.* *67*, 4017-4026, 1993.) NS4A provides a cofactor for NS3 activity. (Failla *et al.*, *J. Virol.* *68*, 3753-3760, 1994, De Francesco *et al.*, U.S. Patent No. 5,739,002.)

NS5A is a highly phosphorylated protein conferring interferon resistance. (De Francesco *et al.*, *Semin. Liver Dis.*, *20*(1), 69-83, 2000, Pawlotsky, *Viral Hepat. Suppl.* *1*, 47-48, 1999.)

NS5B provides an RNA-dependent RNA polymerase. (De Francesco *et al.*, International Publication Number WO 96/37619, Behrens *et al.*, *EMBO* *15*, 12-22, 1996, Lohmann *et al.*, *Virology* *249*, 108-118, 1998.)

SUMMARY OF THE INVENTION

The present invention features Ad6 vectors and a nucleic acid encoding a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide containing an inactive NS5B RNA-dependent RNA polymerase region. The nucleic acid is particularly useful as a component of an adenovector or DNA plasmid vaccine providing a broad range of antigens for generating an HCV specific cell mediated immune (CMI) response against HCV.

A HCV specific CMI response refers to the production of cytotoxic T lymphocytes and T helper cells that recognize an HCV antigen. The CMI response may also include non-HCV specific immune effects.

Preferred nucleic acids encode a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide that is substantially similar to SEQ. ID. NO. 1 and has sufficient protease activity to process itself to produce at least a polypeptide substantially similar to the NS5B region present in SEQ. ID. NO. 1. The produced polypeptide corresponding to NS5B is enzymatically inactive. More preferably, the HCV polypeptide has sufficient

protease activity to produce polypeptides substantially similar to the NS3, NS4A, NS4B, NS5A, and NS5B regions present in SEQ. ID. NO. 1.

Reference to a "substantially similar sequence" indicates an identity of at least about 65% to a reference sequence. Thus, for example, polypeptides having an amino acid sequence substantially similar to SEQ. ID. NO. 1 have an overall amino acid identity of at least about 65% to SEQ. ID. NO. 1.

Polypeptides corresponding to NS3, NS4A, NS4B, NS5A, and NS5B have an amino acid sequence identity of at least about 65% to the corresponding region in SEQ. ID. NO. 1. Such corresponding polypeptides are also referred to herein as NS3, NS4A, NS4B, NS5A, and NS5B polypeptides.

Thus, a first aspect of the present invention describes a nucleic acid comprising a nucleotide sequence encoding a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide substantially similar to SEQ. ID. NO. 1. The encoded polypeptide has sufficient protease activity to process itself to produce an NS5B polypeptide that is enzymatically inactive.

In a preferred embodiment, the nucleic acid is an expression vector capable of expressing the Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide in a desired human cell. Expression inside a human cell has therapeutic applications for actively treating an HCV infection and for prophylactically treating against an HCV infection.

An expression vector contains a nucleotide sequence encoding a polypeptide along with regulatory elements for proper transcription and processing. The regulatory elements that may be present include those naturally associated with the nucleotide sequence encoding the polypeptide and exogenous regulatory elements not naturally associated with the nucleotide sequence. Exogenous regulatory elements such as an exogenous promoter can be useful for expression in a particular host, such as in a human cell. Examples of regulatory elements useful for functional expression include a promoter, a terminator, a ribosome binding site, and a polyadenylation signal.

Another aspect of the present invention describes a nucleic acid comprising a gene expression cassette able to express in a human cell a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide substantially similar to SEQ. ID. NO. 1. The polypeptide can process itself to produce an enzymatically inactive NS5B protein. The gene expression cassette contains at least the following:

a) a promoter transcriptionally coupled to a nucleotide sequence encoding a polypeptide;

b) a 5' ribosome binding site functionally coupled to the nucleotide sequence,

c) a terminator joined to the 3' end of the nucleotide sequence, and

d) a 3' polyadenylation signal functionally coupled to the nucleotide sequence.

Reference to "transcriptionally coupled" indicates that the promoter is positioned such that transcription of the nucleotide sequence can be brought about by RNA polymerase binding at the promoter. Transcriptionally coupled does not require that the sequence being transcribed is adjacent to the promoter.

Reference to "functionally coupled" indicates the ability to mediate an effect on the nucleotide sequence. Functionally coupled does not require that the coupled sequences be adjacent to each other. A 3' polyadenylation signal functionally coupled to the nucleotide sequence facilitates cleavage and polyadenylation of the transcribed RNA. A 5' ribosome binding site functionally coupled to the nucleotide sequence facilitates ribosome binding.

In preferred embodiments the nucleic acid is a DNA plasmid vector or an adenovector suitable for either therapeutic application in treating HCV or as an intermediate in the production of a therapeutic vector. Treating HCV includes actively treating an HCV infection and prophylactically treating against an HCV infection.

Another aspect of the present invention describes an adenovector comprising a Met-NS3-NS4A-NS4B-NS5A-NS5B expression cassette able to express a polypeptide substantially similar to SEQ. ID. NO. 1 that is produced by a process involving (a) homologous recombination and (b) adenovector rescue. The homologous recombinant step produces an adenovirus genome plasmid. The adenovector rescue step produces the adenovector from the adenogenome plasmid.

Adenovirus genome plasmids described herein contain a recombinant adenovirus genome having a deletion in the E1 region and optionally in the E3 region and a gene expression cassette inserted into one of the deleted regions. The recombinant adenovirus genome is made of regions substantially similar to one or more adenovirus serotypes.

Another aspect of the present invention describes an adenovector consisting of the nucleic acid sequence of SEQ. ID. NO. 4 or a derivative thereof,

wherein said derivative thereof has the HCV polyprotein encoding sequence present in SEQ. ID. NO. 4 replaced with the HCV polyprotein encoding sequence of either SEQ. ID. NO. 3, SEQ. ID. NO. 10 or SEQ. ID. NO. 11.

Another aspect of the present invention describes a cultured recombinant cell comprising a nucleic acid containing a sequence encoding a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide substantially similar to SEQ. ID. NO. 1. The recombinant cell has a variety of uses such as being used to replicate nucleic acid encoding the polypeptide in vector construction methods.

Another aspect of the present invention describes a method of making an adenovector comprising a Met-NS3-NS4A-NS4B-NS5A-NS5B expression cassette able to express a polypeptide substantially similar to SEQ. ID. NO. 1. The method involves the steps of (a) producing an adenovirus genome plasmid containing a recombinant adenovirus genome with deletions in the E1 and E3 regions and a gene expression cassette inserted into one of the deleted regions and (b) rescuing the adenovector from the adenovirus genome plasmid.

Another aspect of the present invention describes a pharmaceutical composition comprising a vector for expressing a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide substantially similar to SEQ. ID. NO. 1 and a pharmaceutically acceptable carrier. The vector is suitable for administration and polypeptide expression in a patient.

A "patient" refers to a mammal capable of being infected with HCV. A patient may or may not be infected with HCV. Examples of patients are humans and chimpanzees.

Another aspect of the present invention describes a method of treating a patient comprising the step of administering to the patient an effective amount of a vector expressing a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide substantially similar to SEQ. ID. NO. 1. The vector is suitable for administration and polypeptide expression in the patient.

The patient undergoing treatment may or may not be infected with HCV. For a patient infected with HCV, an effective amount is sufficient to achieve one or more of the following effects: reduce the ability of HCV to replicate, reduce HCV load, increase viral clearance, and increase one or more HCV specific CMI responses. For a patient not infected with HCV, an effective amount is sufficient to achieve one or more of the following: an increased ability to produce one or more components of a HCV specific CMI response to a HCV infection, a reduced

susceptibility to HCV infection, and a reduced ability of the infecting virus to establish persistent infection for chronic disease.

Another aspect of the present invention features a recombinant nucleic acid comprising an Ad6 region and a region not present in Ad6. Reference to "recombinant" nucleic acid indicates the presence of two or more nucleic acid regions not naturally associated with each other. Preferably, the Ad6 recombinant nucleic acid contains Ad6 regions and a gene expression cassette coding for a polypeptide heterologous to Ad6.

Other features and advantages of the present invention are apparent from the additional descriptions provided herein including the different examples. The provided examples illustrate different components and methodology useful in practicing the present invention. The examples do not limit the claimed invention. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B illustrate SEQ. ID. NO. 1.

Figures 2A, 2B, 2C, and 2D illustrate SEQ. ID. NO. 2. SEQ. ID. NO. 2 provides a nucleotide sequence coding for SEQ. ID. NO. 1 along with an optimized internal ribosome entry site and TAAA termination. Nucleotides 1-6 provides an optimized internal ribosome entry site. Nucleotides 7-5961 code for a HCV Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide with nucleotides in positions 5137 to 5145 providing a AlaAlaGly sequence in amino acid positions 1711 to 1713 that renders NS5B inactive. Nucleotides 5962-5965 provide a TAAA termination.

Figures 3A, 3B, 3C, and 3D illustrate SEQ. ID. NO. 3. SEQ. ID. NO. 3 is a codon optimized version of SEQ. ID. NO. 2. Nucleotides 7-5961 encode a HCV Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide.

Figures 4A-4M illustrate MRKAd6-NSmut (SEQ. ID. NO. 4). SEQ. ID. NO. 4 is an adenovector containing an expression cassette where the polypeptide of SEQ. ID. NO. 1 is encoded by SEQ. ID. NO. 2. Base pairs 1-450 correspond to the Ad5 bp 1 to 450; base pairs 462 to 1252 correspond to the human CMV promoter; base pairs 1258 to 1267 correspond to the Kozak sequence; base pairs 1264 to 7222 correspond to the NS genes; base pairs 7231 to 7451 correspond to the BGH polyadenylation signal; base pairs 7469 to 9506 correspond to Ad5 base pairs 3511 to 5548; base pairs 9507 to 32121 correspond to Ad6 base pairs 5542 to 28156; base

pairs 32122 to 35117 correspond to Ad6 base pairs 30789 to 33784; and base pairs 35118 to 37089 correspond to Ad5 base pairs 33967 to 35935.

Figures 5A-5O illustrate SEQ. ID. NOs. 5 and 6. SEQ. ID. NO. 5 encodes a HCV Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide with an active RNA dependent RNA polymerase. SEQ. ID. NO. 6 provides the amino acid sequence for the polypeptide.

Figures 6A-6C provide the nucleic acid sequence for pV1JnsA (SEQ. ID. NO. 7).

Figures 7A-7N provide the nucleic acid sequence for the Ad6 genome (SEQ. ID. NO. 8).

Figures 8A-8K provide the nucleic acid sequence for the Ad5 genome (SEQ. ID. NO. 9).

Figure 9 illustrates different regions of the Ad6 genome. The linear (35759 bp) ds DNA genome is indicated by two parallel lines and is divided into 100 map units. Transcription units are shown relative to their position and orientation in the genome. Early genes (E1A, E1B, E2A/B, E3 and E4 are indicated by gray arrows. Late genes (L1 to L5) , indicated by black arrows, are produced by alternative splicing of a transcript produced from the major late promoter (MLP) and all contain the tripartite leader (1, 2, 3) at their 5' ends. The E1 region is located from approximately 1.0 to 11.5 map units, the E2 region from 75.0 to 11.5 map units, E3 from 76.1 to 86.7 map units, and E4 from 99.5 to 91.2 map units. The major late transcription unit is located between 16.0 and 91.2 map units.

Figure 10 illustrates homologous recombination to recover pAdE1-E3+ containing Ad6 and Ad5 regions.

Figure 11 illustrates homologous recombinant to recover a pAdE1-E3+ containing Ad6 regions.

Figure 12 illustrates a western blot on whole-cell extracts from 293 cells transfected with plasmid DNA expressing different HCV NS cassettes. Mature NS3 and NS5A products were detected with specific antibodies. "pV1Jns-NS" refers to a pV1JnsA plasmid where a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide is encoded by SEQ. ID. NO. 5, and SEQ. ID. NO. 5 is inserted between bases 1881 and 1912 of SEQ. ID. NO. 7. "pV1Jns-NSmut" refers to a pV1JnsA plasmid where SEQ. ID. NO. 2 is inserted between bases 1882 and 1925 of SEQ. ID. NO. 7. "pV1Jns-NSOPTmut" refers to a pV1JnsA plasmid where SEQ. ID. NO. 3 is inserted between bases 1881 and 1905 of SEQ. ID. NO. 7.

Figures 13A and 13B illustrate T cell responses by IFNγ ELIspot induced in C57black6 mice (A) and BalbC mice (B) by two injections of 25μg and 50μg, respectively, of plasmid DNA encoding the different HCV NS cassettes with Gene Electro-Transfer (GET).

Figure 14 illustrates protein expression from different adenovectors upon infection of HeLa cells. MRKAd5-NSmut is an adenovector based on an Ad5 sequence (SEQ. ID. NO. 9), where the Ad5 genome has an E1 deletion of base pairs 451 to 3510, an E3 deletion of base pairs 28134 to 30817, and has the NS3-NS4A-NS4B-NS5A-NS5B expression cassette as provided in base pairs 451 to 7468 of SEQ. ID. NO. 4 inserted between positions 450 and 3511. Ad5-NS is an adenovector based on an Ad5 backbone with an E1 deletion of base pairs 342 to 3523, and E3 deletion of base pairs 28134 to 30817 and containing an expression cassette encoding a NS3-NS4A-NS4B-NS5A-NS5B from SEQ. ID. NO. 5. "MRKAd6-NSOPTmut" refers to an adenovector having a modified SEQ. ID. NO. 4 sequence, wherein base pairs 1258 to 7222 of SEQ. ID. NO. 4 is replaced with SEQ. ID. NO. 3.

Figure 15 illustrates T cell responses by IFNγ ELIspot induced in C57black6 mice by two injections of 10^9 vp of adenovectors containing different HCV non-structural gene cassettes.

Figures 16A-16D illustrate T cell responses by IFNγ ELIspot induced in Rhesus monkeys by one or two injections of 10^{10} vp (A) or 10^{11} vp (B) of adenovectors containing different HCV non-structural gene cassettes.

Figures 17A and 17B illustrates CD8+ T cell responses by IFNγ ICS induced in Rhesus monkeys by two injections of 10^{10} vp (A) or 10^{11} vp (B) of adenovectors encoding the different HCV non-structural gene cassettes.

Figures 18A-18F illustrate T cell responses by bulk CTL assay induced in Rhesus monkeys by two injections of 10^{11} vp of Ad5-NS (A), MRKAd5-NSmut (B), or MRKAd6-NSmut (C).

Figure 19 illustrates the plasmid pE2.

Figures 20A-D illustrates the partial codon optimized sequence NSsuboptmut (SEQ. ID. NO. 10). Coding sequence for the Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide is from base 7 to 5961.

DETAILED DESCRIPTION OF THE INVENTION

The present invention features Ad6 vectors and nucleic acid encoding a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide that contains an inactive NS5B region. Providing an inactive NS5B region supplies NS5B antigens while reducing the possibility of adverse side effects due to an active viral RNA polymerase. Uses of the featured nucleic acid include use as a vaccine component to introduce into a cell an HCV polypeptide that provides a broad range of antigens for generating a CMI response against HCV, and as an intermediate for producing such a vaccine component.

The adaptive cellular immune response can function to recognize viral antigens in HCV infected cells throughout the body due to the ubiquitous distribution of major histocompatibility complex (MHC) class I and II expression, to induce immunological memory, and to maintain immunological memory. These functions are attributed to antigen-specific CD4+ T helper (Th) and CD8+ cytotoxic T cells (CTL).

Upon activation via their specific T cell receptors, HCV specific Th cells fulfill a variety of immunoregulatory functions, most of them mediated by Th1 and Th2 cytokines. HCV specific Th cells assist in the activation and differentiation of B cells and induction and stimulation of virus-specific cytotoxic T cells. Together with CTL, Th cells may also secrete IFN-γ and TNF-α that inhibit replication and gene expression of several viruses. Additionally, Th cells and CTL, the main effector cells, can induce apoptosis and lysis of virus infected cells.

HCV specific CTL are generated from antigens processed by professional antigen presenting cells (pAPCs). Antigens can be either synthesized within or introduced into pAPCs. Antigen synthesis in a pAPC can be brought about by introducing into the cell an expression cassette encoding the antigen.

A preferred route of nucleic acid vaccine administration is an intramuscular route. Intramuscular administration appears to result in the introduction and expression of nucleic acid into somatic cells and pAPCs. HCV antigens produced in the somatic cells can be transferred to pAPCs for presentation in the context of MHC class I molecules. (Donnelly *et al.*, *Annu. Rev. Immunol.* *15*:617-648, 1997.)

pAPCs process longer length antigens into smaller peptide antigens in the proteasome complex. The antigen is translocated into the endoplasmic reticulum/Golgi complex secretory pathway for association with MHC class I

proteins. CD8+ T lymphocytes recognize antigen associated with class I MHC via the T cell receptor (TCR) and the CD8 cell surface protein.

Using a nucleic acid encoding a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide as a vaccine component allows for production of a broad range of antigens capable of generating CMI responses from a single vector. The polypeptide should be able to process itself sufficiently to produce at least a region corresponding to NS5B. Preferred nucleic acids encode an amino acid sequence substantially similar to SEQ. ID. NO. 1 that has sufficient protease activity to process itself to produce individual HCV polypeptides substantially similar to the NS3, NS4A, NS4B, NS5A, and NS5B regions present in SEQ. ID. NO. 1.

A polypeptide substantially similar to SEQ. ID. NO. 1 with sufficient protease activity to process itself in a cell provides the cell with T cell epitopes that are present in several different HCV strains. Protease activity is provided by NS3 and NS3/NS4A proteins digesting the Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide at the appropriate cleavage sites to release polypeptides corresponding to NS3, NS4A, NS4B, NS5A, and NS5B. Self- processing of the Met-NS3-NS4A-NS4B-NS5A-NS5B generates polypeptides that approximate naturally occurring HCV polypeptides.

Based on the guidance provided herein a sufficiently strong immune response can be generated to achieve beneficial effects in a patient. The provided guidance includes information concerning HCV sequence selection, vector selection, vector production, combination treatment, and administration.

I. HCV SEQUENCES

A variety of different nucleic acid sequences can be used as a vaccine component to supply a HCV Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide to a cell or as an intermediate to produce vaccine components. The starting point for obtaining suitable nucleic acid sequences are preferably naturally occurring NS3-NS4A-NS4B-NS5A-NS5B polypeptide sequences modified to produce an inactive NS5B.

The use of a HCV nucleic acid sequence providing HCV non-structural antigens to generate a CMI response is mentioned by Cho *et al.*, *Vaccine 17*:1136-1144, 1999, Paliard *et al.*, International Publication Number WO 01/30812 (not admitted to be prior art to the claimed invention), and Coit *et al.*, International Publication Number WO 01/38360 (not admitted to be prior art to the claimed invention). Such references fail to describe, for example, a polypeptide that processes

itself to produce an inactive NS5B, and the particular combinations of HCV sequences and delivery vehicles employed herein.

Modifications to a HCV Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide sequence can be produced by altering the encoding nucleic acid. Alterations can be performed to create deletions, insertions and substitutions.

Small modifications can be made in NS5B to produce an inactive polymerase by targeting motifs essentially for replication. Examples of motifs critical for NS5B activity and modifications that can be made to produce an inactive NS5B are described by Lohmann *et al., Journal of Virology 71*:8416-8426, 1997, and Kolykhalov *et al., Journal of Virology 74*:2046-2051, 2000.

Additional factors to take into account when producing modifications to a HCV Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide include maintaining the ability to self-process and maintaining T cell antigens. The ability of the HCV polypeptide to process itself is determined to a large extent by a functional NS3 protease. Modifications that maintain NS3 activity protease activity can be obtained by taking into account the NS3 protein, NS4A which serves as a cofactor for NS3, and NS3 protease recognition sites present within the NS3-NS4A-NS4B-NS5A-NS5B polypeptide.

Different modifications can be made to naturally occurring NS3-NS4A-NS4B-NS5A-NS5B polypeptide sequences to produce polypeptides able to elicit a broad range of T cell responses. Factors influencing the ability of a polypeptide to elicit a broad T cell response include the preservation or introduction of HCV specific T cell antigen regions and prevalence of different T cell antigen regions in different HCV isolates.

Numerous examples of naturally occurring HCV isolates are well known in the art. HCV isolates can be classified into the following six major genotypes comprising one or more subtypes: HCV-1/(1a,1b,1c), HCV-2/(2a,2b,2c), HCV-3/(3a,3b,10a), HCV-4/(4a), HCV-5/(5a) and HCV-6/(6a,6b,7b,8b,9a,11a). (Simmonds, *J. Gen. Virol.,* 693-712, 2001.) Examples of particular HCV sequences such as HCV-BK, HCV-J, HCV-N, HCV-H, have been deposited in GenBank and described in various publications. (See, for example, Chamberlain *et al.*; *J. Gen. Virol.*, 1341-1347, 1997.)

HCV T cell antigens can be identified by, for example, empirical experimentation. One way of identifying T cell antigens involves generating a series of overlapping short peptides from a longer length polypeptide and then screening the

T-cell populations from infected patients for positive clones. Positive clones are activated/primed by a particular peptide. Techniques such as IFNγ-ELISPOT, IFNγ-Intracellular staining and bulk CTL assays can be used to measure peptide activity. Peptides thus identified can be considered to represent T-cell epitopes of the respective pathogen.

HCV T cell antigen regions from different HCV isolates can be introduced into a single sequence by, for example, producing a hybrid NS3-NS4A-NS4B-NS5A-NS5B polypeptide containing regions from two or more naturally occurring sequences. Such a hybrid can contain additional modifications, which preferably do not reduce the ability of the polypeptide to produce an HCV CMI response.

The ability of a modified Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide to process itself and produce a CMI response can be determined using techniques described herein or well known in the art. Such techniques include the use of IFNγ-ELISPOT, IFNγ-Intracellular staining and bulk CTL assays to measure a HCV specific CMI response.

A. Met-NS3-NS4A-NS4B-NS5A-NS5B Sequences

SEQ. ID. NO. 1 provides a preferred Met-NS3-NS4A-NS4B-NS5A-NS5B sequence. SEQ. ID. NO. 1 contains a large number of HCV specific T cell antigens that are present in several different HCV isolates. SEQ. ID. NO. 1 is similar to the NS3-NS4A-NS4B-NS5A-NS5B portion of the HCV BK strain nucleotide sequence (GenBank accession number M58335).

In SEQ. ID. NO. 1 anchor positions important for recognition by MHC class I molecules are conserved or represent conservative substitutions for 18 out of 20 known T-cell epitopes in the NS3-NS4A-NS4B-NS5A-NS5B portion of HCV polyproteins. With respect to the remaining two known T-cell epitopes, one has a non-conservative anchor substitution in SEQ. ID. NO. 1 that may still be recognized by a different HLA supertype and one epitope has one anchor residue not conserved. HCV T-cell epitopes are described in Chisari *et al.*, *Curr. Top. Microbiol Immunol.*, *242*:299-325, 2000, and Lechner et al. *J. Exp. Med.* *9*:1499-1512, 2000.

Differences between the HCV-BK NS3-NS4A-NS4B-NS5A-NS5B nucleotide sequence and SEQ. ID. NO. 1 include the introduction of a methionine at the 5' end and the presence of modified NS5B active site residues in SEQ. ID. NO. 1.

The modification replaces GlyAspAsp with AlaAlaGly (residues 1711-1713) to inactivate NS5B.

The encoded HCV Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide preferably has an amino acid sequence substantially similar to SEQ. ID. NO. 1. In different embodiments, the encoded HCV Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide has an amino acid identify to SEQ. ID. NO. 1 of at least 65%, at least 75%, at least 85%, at least 95%, at least 99% or 100%; or differs from SEQ. ID. NO. 1 by 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 1-11, 1-12, 1-13, 1-14, 1-15, 1-16, 1-17, 1-18, 1-19, or 1-20 amino acids.

Amino acid differences between a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide and SEQ. ID. NO. 1 are calculated by determining the minimum number of amino acid modifications in which the two sequences differ. Amino acid modifications can be deletions, additions, substitutions or any combination thereof.

Amino acid sequence identity is determined by methods well known in the art that compare the amino acid sequence of one polypeptide to the amino acid sequence of a second polypeptide and generate a sequence alignment. Amino acid identity is calculated from the alignment by counting the number of aligned residue pairs that have identical amino acids.

Methods for determining sequence identity include those described by Schuler, G.D. in *Bioinformatics: A Practical Guide to the Analysis of Genes and Proteins*, Baxevanis, A.D. and Ouelette, B.F.F., eds., John Wiley & Sons, Inc, 2001; Yona, *et al.*, in *Bioinformatics: Sequence, structure and databanks*, Higgins, D. and Taylor, W. eds, Oxford University Press, 2000; and *Bioinformatics: Sequence and Genome Analysis*, Mount, D.W., ed., Cold Spring Harbor Laboratory Press, 2001). Methods to determine amino acid sequence identity are codified in publicly available computer programs such as GAP (Wisconsin Package Version 10.2, Genetics Computer Group (GCG), Madison, Wisc.), BLAST (Altschul *et al.*, *J. Mol. Biol. 215(3)*:403-10, 1990), and FASTA (Pearson, *Methods in Enzymiology 183*:63-98, 1990, R.F. Doolittle, ed.).

In an embodiment of the present invention sequence identity between two polypeptides is determined using the GAP program (Wisconsin Package Version 10.2, Genetics Computer Group (GCG), Madison, Wisc.). GAP uses the alignment method of Needleman and Wunsch. (Needleman, *et al.*, *J. Mol. Biol. 48*:443-453, 1970.) GAP considers all possible alignments and gap positions between two sequences and creates a global alignment that maximizes the number of matched

residues and minimizes the number and size of gaps. A scoring matrix is used to assign values for symbol matches. In addition, a gap creation penalty and a gap extension penalty are required to limit the insertion of gaps into the alignment. Default program parameters for polypeptide comparisons using GAP are the BLOSUM62 (Henikoff *et al., Proc. Natl. Acad. Sci. USA, 89*:10915-10919, 1992) amino acid scoring matrix (MATrix=blosum62.cmp), a gap creation parameter (GAPweight=8) and a gap extension pararameter (LENgthweight=2).

More preferred HCV Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptides in addition to being substantially similar to SEQ. ID. NO. 1 across their entire length produce individual NS3, NS4A, NS4B, NS5A and NS5B regions that are substantially similar to the corresponding regions present in SEQ. ID. NO. 1. The corresponding regions in SEQ. ID. NO. 1 are provided as follows: Met-NS3 amino acids 1-632; NS4A amino acids 633-686; NS4B amino acids 687-947; NS5A amino acids 948-1394; and NS5B amino acids 1395-1985.

In different embodiments a NS3, NS4A, NS4B, NS5A and/or NS5B region has an amino acid identity to the corresponding region in SEQ. ID. NO. 1 of at least 65%, at least 75%, at least 85%, at least 95%, at least 99%, or 100%; or an amino acid difference of 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 1-11, 1-12, 1-13, 1-14, 1-15, 1-16, 1-17, 1-18, 1-19, or 1-20 amino acids.

Amino acid modifications to SEQ. ID. NO. 1 preferably maintain all or most of the T-cell antigen regions. Differences in naturally occurring amino acids are due to different amino acid side chains (R groups). An R group affects different properties of the amino acid such as physical size, charge, and hydrophobicity. Amino acids can be divided into different groups as follows: neutral and hydrophobic (alanine, valine, leucine, isoleucine, proline, tyrptophan, phenylalanine, and methionine); neutral and polar (glycine, serine, threonine, tryosine, cysteine, asparagine, and glutamine); basic (lysine, arginine, and histidine); and acidic (aspartic acid and glutamic acid).

Generally, in substituting different amino acids it is preferable to exchange amino acids having similar properties. Substituting different amino acids within a particular group, such as substituting valine for leucine, arginine for lysine, and asparagine for glutamine are good candidates for not causing a change in polypeptide tertiary structure.

Starting with a particular amino acid sequence and the known degeneracy of the genetic code, a large number of different encoding nucleic acid

sequences can be obtained. The degeneracy of the genetic code arises because almost all amino acids are encoded by different combinations of nucleotide triplets or "codons". The translation of a particular codon into a particular amino acid is well known in the art (*see, e.g.*, Lewin *GENES IV*, p. 119, Oxford University Press, 1990). Amino acids are encoded by codons as follows:

A=Ala=Alanine: codons GCA, GCC, GCG, GCU
C=Cys=Cysteine: codons UGC, UGU
D=Asp=Aspartic acid: codons GAC, GAU
E=Glu=Glutamic acid: codons GAA, GAG
F=Phe=Phenylalanine: codons UUC, UUU
G=Gly=Glycine: codons GGA, GGC, GGG, GGU
H=His=Histidine: codons CAC, CAU
I=Ile=Isoleucine: codons AUA, AUC, AUU
K=Lys=Lysine: codons AAA, AAG
L=Leu=Leucine: codons UUA, UUG, CUA, CUC, CUG, CUU
M=Met=Methionine: codon AUG
N=Asn=Asparagine: codons AAC, AAU
P=Pro=Proline: codons CCA, CCC, CCG, CCU
Q=Gln=Glutamine: codons CAA, CAG
R=Arg=Arginine: codons AGA, AGG, CGA, CGC, CGG, CGU
S=Ser=Serine: codons AGC, AGU, UCA, UCC, UCG, UCU
T=Thr=Threonine: codons ACA, ACC, ACG, ACU
V=Val=Valine: codons GUA, GUC, GUG, GUU
W=Trp=Tryptophan: codon UGG
Y=Tyr=Tyrosine: codons UAC, UAU.

Nucleic acid sequences can be optimized in an effort to enhance expression in a host. Factors to be considered include C:G content, preferred codons, and the avoidance of inhibitory secondary structure. These factors can be combined in different ways in an attempt to obtain nucleic acid sequences having enhanced expression in a particular host. (See, for example, Donnelly *et al.*, International Publication Number WO 97/47358.)

The ability of a particular sequence to have enhanced expression in a particular host involves some empirical experimentation. Such experimentation involves measuring expression of a prospective nucleic acid sequence and, if needed, altering the sequence.

B. Encoding Nucleotide Sequences

SEQ. ID. NOs. 2 and 3 provide two examples of nucleotide sequences encoding a Met-NS3-NS4A-NS4B-NS5A-NS5B sequence. The coding sequence of SEQ. ID. NO. 2 is similar (99.4% nucleotide sequence identity) to the NS3-NS4A-NS4B-NS5A-NS5B region of the naturally occurring HCV-BK sequence (GenBank accession number M58335). SEQ. ID. NO. 3 is a codon-optimized version of SEQ. ID. NO. 2. SEQ. ID. NOs. 2 and 3 have a nucleotide sequence identity of 78.3%.

Differences between the HCV-BK NS3-NS4A-NS4B-NS5A-NS5B nucleotide (GenBank accession number M58335) and SEQ. ID. NO. 2, include SEQ. ID. NO. 2 having a ribosome binding site, an ATG methionine codon, a region coding for a modified NS5B catalytic domain, a TAAA stop signal and an additional 30 nucleotide differences. The modified catalytic domain codes for a AlaAlaGly (residues 1711-1713) instead of GlyAspAsp to inactivate NS5B.

A nucleotide sequence encoding a HCV Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide is preferably substantially similar to the SEQ. ID. NO. 2 coding region. In different embodiments, the nucleotide sequence encoding a HCV Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide has a nucleotide sequence identify to the SEQ. ID. NO. 2 coding region of at least 65%, at least 75%, at least 85%, at least 95%, at least 99%, or 100%; or differs from SEQ. ID. NO. 2 by 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 1-11, 1-12, 1-13, 1-14, 1-15, 1-16, 1-17, 1-18, 1-19, 1-20, 1-25, 1-30, 1-35, 1-40, 1-45, or 1-50 nucleotides.

Nucleotide differences between a sequence coding Met-NS3-NS4A-NS4B-NS5A-NS5B and the SEQ. ID. NO. 2 coding region are calculated by determining the minimum number of nucleotide modifications in which the two sequences differ. Nucleotide modifications can be deletions, additions, substitutions or any combination thereof.

Nucleotide sequence identity is determined by methods well known in the art that compare the nucleotide sequence of one sequence to the nucleotide sequence of a second sequence and generate a sequence alignment. Sequence identity is determined from the alignment by counting the number of aligned positions having identical nucleotides.

Methods for determining nucleotide sequence identity between two polynucleotides include those described by Schuler, in *Bioinformatics: A Practical Guide to the Analysis of Genes and Proteins*, Baxevanis, A.D. and Ouelette, B.F.F.,

eds., John Wiley & Sons, Inc, 2001; Yona *et al.*,. in *Bioinformatics: Sequence, structure and databanks*, Higgins, D. and Taylor, W. eds, Oxford University Press, 2000; and *Bioinformatics: Sequence and Genome Analysis*, Mount, D.W., ed., Cold Spring Harbor Laboratory Press, 2001). Methods to determine nucleotide sequence identity are codified in publicly available computer programs such as GAP (Wisconsin Package Version 10.2, Genetics Computer Group (GCG), Madison, Wisc.), BLAST (Altschul *et al.*, *J. Mol. Biol. 215(3)*:403-10, 1990), and FASTA (Pearson, W.R., *Methods in Enzymology 183*:63-98, 1990, R.F. Doolittle, ed.).

In an embodiment of the present ivnention, sequence identity between two polynucleotides is determined by application of GAP (Wisconsin Package Version 10.2, Genetics Computer Group (GCG), Madison, Wisc.). GAP uses the alignment method of Needleman and Wunsch. (Needleman *et al., J. Mol. Biol. 48*:443-453, 1970.) GAP considers all possible alignments and gap positions between two sequences and creates a global alignment that maximizes the number of matched residues and minimizes the number and size of gaps. A scoring matrix is used to assign values for symbol matches. In addition, a gap creation penalty and a gap extension penalty are required to limit the insertion of gaps into the alignment. Default program parameters for polynucleotide comparisons using GAP are the nwsgapdna.cmp scoring matrix (MATrix=nwsgapdna.cmp), a gap creation parameter (GAPweight=50) and a gap extension pararameter (LENgthweight=3).

More preferred HCV Met-NS3-NS4A-NS4B-NS5A-NS5B nucleotide sequences in addition to being substantially similar across its entire length, produce individual NS3, NS4A, NS4B, NS5A and NS5B regions that are substantially similar to the corresponding regions present in SEQ. ID. NO. 2. The corresponding coding regions in SEQ. ID. NO. 2 are provided as follows: Met-NS3, nucleotides 7-1902; NS4A nucleotides 1903-2064; NS4B nucleotides 2065-2847; NS5A nucleotides 2848-4188: NS5B nucleotides 4189-5661.

In different embodiments a NS3, NS4A, NS4B, NS5A and/or NS5B encoding region has a nucleotide sequence identity to the corresponding region in SEQ. ID. NO. 2 of at least 65%, at least 75%, at least 85%, at least 95%, at least 99% or 100%; or a nucleotide difference to SEQ. ID. NO. 2 of 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 1-11, 1-12, 1-13, 1-14, 1-15, 1-16, 1-17, 1-18, 1-19, 1-20, 1-25, 1-30, 1-35, 1-40, 1-45, or 1-50 nucleotides.

C. Gene Expression Cassettes

A gene expression cassette contains elements needed for polypeptide expression. Reference to "polypeptide" does not provide a size limitation and includes protein. Regulatory elements present in a gene expression cassette generally include: (a) a promoter transcriptionally coupled to a nucleotide sequence encoding the polypeptide, (b) a 5' ribosome binding site functionally coupled to the nucleotide sequence, (c) a terminator joined to the 3' end of the nucleotide sequence, and (d) a 3' polyadenylation signal functionally coupled to the nucleotide sequence. Additional regulatory elements useful for enhancing or regulating gene expression or polypeptide processing may also be present.

Promoters are genetic elements that are recognized by an RNA polymerase and mediate transcription of downstream regions. Preferred promoters are strong promoters that provide for increased levels of transcription. Examples of strong promoters are the immediate early human cytomegalovirus promoter (CMV), and CMV with intron A. (Chapman *et al, Nucl. Acids Res.* 19:3979-3986, 1991.) Additional examples of promoters include naturally occurring promoters such as the EF1 alpha promoter, the murine CMV promoter, Rous sarcoma virus promoter, and SV40 early/late promoters and the β-actin promoter; and artificial promoters such as a synthetic muscle specific promoter and a chimeric muscle-specific/CMV promoter (Li *et al., Nat. Biotechnol. 17*:241-245, 1999, Hagstrom *et al., Blood 95*:2536-2542, 2000).

The ribosome binding site is located at or near the initiation codon. Examples of preferred ribosome binding sites include CCACCAUGG, CCGCCAUGG, and ACCAUGG, where AUG is the initiation codon. (Kozak, *Cell 44*:283-292, 1986). Another example of a ribosome binding site is GCCACCAUGG (SEQ. ID. NO. 12).

The polyadenylation signal is responsible for cleaving the transcribed RNA and the addition of a poly (A) tail to the RNA. The polyadenylation signal in higher eukaryotes contains an AAUAAA sequence about 11-30 nucleotides from the polyadenylation addition site. The AAUAAA sequence is involved in signaling RNA cleavage. (Lewin, Genes IV, Oxford University Press, NY, 1990.) The poly (A) tail is important for the mRNA processing.

Polyadenylation signals that can be used as part of a gene expression cassette include the minimal rabbit β -globin polyadenylation signal and the bovine growth hormone polyadenylation (BGH). (Xu *et al., Gene 272*:149-156, 2001, Post *et.*

al., U.S. Patent U. S. 5,122,458.) Additional examples include the Synthetic Polyadenylation Signal (SPA) and SV40 polyadenylation signal. The SPA sequence is as follows: AAUAAAAGAUCUUUAUUUUCAUUAGAUCUGUGUG UUGGUUUUUUGUGUG (SEQ. ID. NO. 13).

Examples of additional regulatory elements useful for enhancing or regulating gene expression or polypeptide processing that may be present include an enhancer, a leader sequence and an operator. An enhancer region increases transcription. Examples of enhancer regions include the CMV enhancer and the SV40 enhancer. (Hitt *et al.*, *Methods in Molecular Genetics* *7*:13-30, 1995, Xu, *et al.*, *Gene 272*:149-156, 2001.) An enhancer region can be associated with a promoter.

A leader sequence is an amino acid region on a polypeptide that directs the polypeptide into the proteasome. Nucleic acid encoding the leader sequence is 5' of a structural gene and is transcribed along the structural gene. An example of a leader sequences is tPA.

An operator sequence can be used to regulate gene expression. For example, the Tet operator sequence can be used to repress gene expression.

II. THERAPEUTIC VECTORS

Nucleic acid encoding a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide can be introduced into a patient using vectors suitable for therapeutic administration. Suitable vectors can deliver nucleic acid into a target cell without causing an unacceptable side effect.

Cellular expression is achieved using a gene expression cassette encoding a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide. The gene expression cassette contains regulatory elements for producing and processing a sufficient amount of nucleic acid inside a target cell to achieve a beneficial effect.

Examples of vectors that can be used for therapeutic applications include first and second generation adenovectors, helper dependent adenovectors, adeno-associated viral vectors, retroviral vectors, alpha virus vectors, Venezuelan Equine Encephalitis virus vector, and plasmid vectors. (Hitt, *et al.*, *Advances in Pharmacology 40*:137-206, 1997, Johnston *et al.*, U.S. Patent No. 6,156,588; and Johnston *et al.*, International Publication Number WO 95/32733.) Preferred vectors for introducing a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide into a subject are first generation adenoviral vectors and plasmid DNA vectors.

A. First Generation Adenovectors

First generation adenovector for expressing a gene expression cassette contain the expression cassette in an E1 and optionally E3 deleted recombinant adenovirus genome. The deletion in the E1 region is sufficiently large to remove elements needed for adenoviral replication.

First generation adenovectors for expressing a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide contain a E1 and E3 deleted recombinant adenovirus genome. The deletion in the E1 region is sufficiently large to remove elements needed for adenoviral replication. The combinations of deletions of the E1 and E3 regions are sufficiently large to accommodate a gene expression cassette encoding a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide.

The adenovirus has a double-stranded linear genome with inverted terminal repeats at both ends. During viral replication, the genome is packaged inside a viral capsid to form a virion. The virus enters its target cell through viral attachment followed by internalization. (Hitt *et al., Advances in Pharmacology 40*:137-206, 1997.)

Adenovectors can be based on different adenovirus serotypes such as those found in humans or animals. Examples of animal adenoviruses include bovine, porcine, chimp, murine, canine, and avian (CELO). Preferred adenovectors are based on human serotypes, more preferably Group B, C, or D serotypes. Examples of human adenovirus Group B, C, D, or E serotypes include types 2 ("Ad2"), 4 ("Ad4"), 5 ("Ad5"), 6 ("Ad6"), 24 ("Ad24"), 26 ("Ad26"), 34 ("Ad34") and 35 ("Ad35"). Adenovectors can contain regions from a single adenovirus or from two or more adenovirus.

In different embodiments adenovectors are based on Ad5, Ad6, or a combination thereof. Ad5 is described by Chroboczek, *et al., J. Virology 186*:280-285, 1992. Ad6 is described in Figures 7A-7N. An Ad6 based vector containing Ad5 regions is described in the Example section provided below.

Adenovectors do not need to have their E1 and E3 regions completely removed. Rather, a sufficient amount the E1 region is removed to render the vector replication incompetent in the absence of the E1 proteins being supplied in *trans*; and the E1 deletion or the combination of the E1 and E3 deletions are sufficiently large enough to accommodate a gene expression cassette.

E1 deletions can be obtained starting at about base pair 342 going up to about base pair 3523 of Ad5, or a corresponding region from other adenoviruses.

Preferably, the deleted region involves removing a region from about base pair 450 to about base pair 3511 of Ad5, or a corresponding region from other adenoviruses. Larger E1 region deletions starting at about base pair 341 removes elements that facilitate virus packaging.

E3 deletions can be obtained starting at about base pair 27865 to about base pair 30995 of Ad5, or the corresponding region of other adenovectors. Preferably the deletion region involves removing a region from about base pair 28134 up to about base pair 30817 of Ad5, or the corresponding region of other adenovectors.

The combination of deletions to the E1 region and optionally the E3 region should be sufficiently large so that the overall size of the recombinant genome containing the gene expression cassette does not exceed about 105% of the wild type adenovirus genome. For example, as recombinant adenovirus Ad5 genomes increase size above about 105% the genome becomes unstable. (Bett *et al.*, *Journal of Virology 67*:5911-5921, 1993.)

Preferably, the size of the recombinant adenovirus genome containing the gene expression cassette is about 85% to about 105% the size of the wild type adenovirus genome. In different embodiments, the size of the recombinant adenovirus genome containing the expression cassette is about 100% to about 105.2%, or about 100%, the size of the wild type genome.

Approximately 7,500 kb can be inserted into an adenovirus genome with a E1 and E3 deletion. Without any deletion, the Ad5 genome is 35,935 base pairs and the Ad6 genome is 35,759 base pairs.

Replication of first generation adenovectors can be performed by supplying the E1 gene products in *trans*. The E1 gene product can be supplied in *trans*, for example, by using cell lines that have been transformed with the adenovirus E1 region. Examples of cells and cells lines transformed with the adenovirus E1 region are HEK 293 cells, 911 cells, PERC.6™ cells, and transfected primary human aminocytes cells. (Graham *et al.*, *Journal of Virology 36*:59-72, 1977, Schiedner *et al.*, *Human Gene Therapy 11*:2105-2116, 2000, Fallaux *et al.*, *Human Gene Therapy 9*:1909-1917, 1998, Bout *et al.*, U.S. Patent No. 6,033,908.)

A Met-NS3-NS4A-NS4B-NS5A-NS5B expression cassette should be inserted into a recombinant adenovirus genome in the region corresponding to the deleted E1 region or the deleted E3 region. The expression cassette can have a parallel or anti-parallel orientation. In a parallel orientation the transcription direction

of the inserted gene is the same direction as the deleted E1 or E3 gene. In an anti-parallel orientation transcription the opposite strand serves as a template and the transcription direction is in the opposite direction.

In an embodiment of the present invention the adenovector has a gene expression cassette inserted in the E1 deleted region. The vector contains:

a) a first adenovirus region from about base pair 1 to about base pair 450 corresponding to either Ad5 or Ad6;

b) a gene expression cassette in a E1 parallel or E1 anti-parallel orientation joined to the first region;

c) a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to the expression cassette;

d) a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6, joined to the second region;

e) a fourth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, joined to the third region; and

f) a fifth adenovirus region from about base pair 33967 to about base pair 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6 joined to the fourth region.

In another embodiment of the present invention the adenovector has an expression cassette inserted in the E3 deleted region. The vector contains:

a) a first adenovirus region from about base pair 1 to about base pair 450 corresponding to either Ad5 or Ad6;

b) a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to the first region;

c) a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6, joined to the second region;

d) a gene expression cassette in a E3 parallel or E3 anti-parallel orientation joined to the third region;

e) a fourth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, joined to the gene expression cassette; and

f) a fifth adenovirus region from about base pair 33967 to about base pair 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6, joined to the fourth region.

In preferred different embodiments concerning adenovirus regions that are present: (1) the first, second, third, fourth, and fifth region corresponds to Ad5; (2) the first, second, third, fourth, and fifth region corresponds to Ad6; and (3) the first region corresponds to Ad5, the second region corresponds to Ad5, the third region corresponds to Ad6, the fourth region corresponds to Ad6, and the fifth region corresponds to Ad5.

B. DNA Plasmid Vectors

DNA vaccine plasmid vectors contain a gene expression cassette along with elements facilitating replication and preferably vector selection. Preferred elements provide for replication in non-mammalian cells and a selectable marker. The vectors should not contain elements providing for replication in human cells or for integration into human nucleic acid.

The selectable marker facilitates selection of nucleic acids containing the marker. Preferred selectable markers are those that confer antibiotic resistance. Examples of antibiotic selection genes include nucleic acid encoding resistance to ampicillin, neomycin, and kanamycin.

Suitable DNA vaccine vectors can be produced starting with a plasmid containing a bacterial origin of replication and a selectable marker. Examples of bacterial origins of replication providing for higher yields include the ColE1 plasmid-derived bacterial origin of replication. (Donnelly *et al., Annu. Rev. Immunol. 15*:617-648, 1997.)

The presence of the bacterial origin of replication and selectable marker allows for the production of the DNA vector in a bacterial strain such as *E. coli*. The selectable marker is used to eliminate bacteria not containing the DNA vector.

III. AD6 RECOMBINANT NUCLEIC ACID

Ad6 recombinant nucleic acid comprises an Ad6 region substantially similar to an Ad6 region found in SEQ. ID. NO. 8, and a region not present in Ad6 nucleic acid. Recombinant nucleic acid comprising Ad6 regions have different uses such as in producing different Ad6 regions, as intermediates in the production of Ad6 based vectors, and as a vector for delivering a recombinant gene.

As depicted in Figure 9, the genomic organization of Ad6 is very similar to the genomic organization of Ad5. The homology between Ad5 and Ad6 is approximately 98%.

In different embodiments, the Ad6 recombinant nucleic acid comprises a nucleotide region substantially similar to E1A, E1B, E2B, E2A, E3, E4, L1, L2, L3, or L4, or any combination thereof. A substantially similar nucleic acid region to an Ad6 region has a nucleotide sequence identity of at least 65%, at least 75%, at least 85%, at least 95%, at least 99% or 100%; or a nucleotide difference of 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 1-11, 1-12, 1-13, 1-14, 1-15, 1-16, 1-17, 1-18, 1-19, 1-20, 1-25, 1-30, 1-35, 1-40, 1-45, or 1-50 nucleotides. Techniques and embodiments for determining substantially similar nucleic acid sequences are described in Section I.B. *supra*.

Preferably, the recombinant Ad6 nucleic acid contains an expression cassette coding for a polypeptide not found in Ad6. Examples of expression cassettes include those coding for HCV regions and those coding for other types of polypeptides.

Different types of adenoviral vectors can be produced incorporating different amounts of Ad6, such as first and second generation adenovectors. As noted in Section II.A. *supra*. first generation adenovectors are defective in E1 and can replicate when E1 is supplied *in trans*.

Second generation adenovectors contain less adenoviral genome than first generation vectors and can be used in conjugation with complementing cell lines and/or helper vectors supplying adenoviral proteins. Second generation adenovectors are described in different references such as Russell, *Journal of General Virology 81*:2573-2604, 2000; Hitt *et al.*, 1997, Human Ad vectors for Gene Transfer, Advances in Pharmacology, Vol 40 Academic Press.

In an embodiment of the present invention, the Ad6 recombinant nucleic acid is an adenovirus vector defective in E1 that is able to replicate when E1 is

supplied *in trans*. Expression cassettes can be inserted into a deleted E1 region and/or a deleted E3 region.

An example of an Ad6 based adenoviral vector with an expression cassette provided in a deleted E1 region comprises or consists of:

a) a first adenovirus region from about base pair 1 to about base pair 450 corresponding to either Ad5 or Ad6;

b) a gene expression cassette in a E1 parallel or E1 anti-parallel orientation joined to the first region;

c) a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to the expression cassette;

d) a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6, joined to the second region;

e) an optionally present fourth region from about base pair 28134 to about base pair 30817 corresponding to Ad5, or from about base pair 28157 to about base pair 30788 corresponding to Ad6, joined to the third region;

f) a fifth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, wherein the fifth region is joined to the fourth region if the fourth region is present, or the fifth is joined to the third region if the fourth region is not present; and

g) a sixth adenovirus region from about base pair 33967 to about base pair 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6, joined to the fifth region;

wherein at least one Ad6 region is present.

In different embodiments of the invention, all of the regions are from Ad6; all of the regions expect for the first and second are from Ad6; and 1, 2, 3, or 4 regions selected from the second, third, fourth, and fifth regions are from Ad6.

An example of an Ad6 based adenoviral vector with an expression cassette provided in a deleted E3 region comprises or consists of:

a) a first adenovirus region from about base pair 1 to about base pair 450 corresponding to either Ad5 or Ad6;

b) a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to the first region;

c) a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6, joined to the second region;

d) a gene expression cassette in a E3 parallel or E3 anti-parallel orientation joined to the third region;

e) a fourth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, joined to the gene expression cassette; and

f) a fifth adenovirus region from about base pair 33967 to about base pair 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6, joined to the fourth region;

wherein at least one Ad6 region is present.

In different embodiment of the invention, all of the regions are from Ad6; all of the regions expect for the first and second are from Ad6; and 1, 2, 3, or 4 regions selected from the second, third, fourth and fifth regions are from Ad6.

IV. VECTOR PRODUCTION

Vectors can be produced using recombinant nucleic acid techniques such as those involving the use of restriction enzymes, nucleic acid ligation, and homologous recombination. Recombinant nucleic acid techniques are well known in the art.. (Ausubel, *Current Protocols in Molecular Biology*, John Wiley, 1987-1998, and Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual*, 2nd Edition, Cold Spring Harbor Laboratory Press, 1989.)

Intermediate vectors are used to derive a therapeutic vector or to transfer an expression cassette or portion thereof from one vector to another vector. Examples of intermediate vectors include adenovirus genome plasmids and shuttle vectors.

Useful elements in an intermediate vector include an origin of replication, a selectable marker, homologous recombination regions, and convenient restriction sites. Convenient restriction sites can be used to facilitate cloning or release of a nucleic acid sequence.

Homologous recombination regions provide nucleic acid sequence regions that are homologous to a target region in another nucleic acid molecule. The homologous regions flank the nucleic acid sequence that is being inserted into the target region. In different embodiments homologous regions are preferably about 150 to 600 nucleotides in length, or about 100 to 500 nucleotides in length.

An embodiment of the present invention describes a shuttle vector containing a Met-NS3-NS4A-NS4B-NS5A-NS5B expression cassette, a selectable marker, a bacterial origin of replication, a first adenovirus homology region and a second adenovirus homologous region that target the expression cassette to insert in or replace an E1 region. The first and second homology regions flank the expression cassette. The first homology region contains at least about 100 base pairs substantially homologous to at least the right end (3' end) of a wild-type adenovirus region from about base pairs 4-450. The second homology contains at least about 100 base pairs substantially homologous to at least the left end (5' end) of Ad5 from about base pairs 3511-5792, or the corresponding region from another adenovirus.

Reference to "substantially homologous" indicates a sufficient degree of homology to specifically recombine with a target region. In different embodiments substantially homologous refers to at least 85%, at least 95%, or 100% sequence identity. Sequence identity can be calculated as described in Section I.B. *supra*.

One method of producing adenovectors is through the creation of an adenovirus genome plasmid containing an expression cassette. The pre-Adenovirus plasmid contains all the adenovirus sequences needed for replication in the desired complimenting cell line. The pre-Adenovirus plasmid is then digested with a restriction enzyme to release the viral ITR's and transfected into the complementing cell line for virus rescue. The ITR's must be released from plasmid sequences to allow replication to occur. Adenovector rescue results in the production on an adenovector containing the expression cassette.

A. Adenovirus Genome Plasmids

Adenovirus genome plasmids contain an adenovector sequence inside a longer-length plasmid (which may be a cosmid). The longer-length plasmid may contain additional elements such as those facilitating growth and selection in eukaryotic or bacterial cells depending upon the procedures employed to produce and maintain the plasmid. Techniques for producing adenovirus genome plasmids include those involving the use of shuttle vectors and homologous recombination, and those

involving the insertion of a gene expression cassette into an adenovirus cosmid. (Hitt *et al., Methods in Molecular Genetics* 7:13-30, 1995, Danthinne *et al., Gene Therapy* 7:1707-1714, 2000.)

Adenovirus genome plasmids preferably have a gene expression cassette inserted into a E1 or E3 deleted region. In an embodiment of the present invention, the adenovirus genome plasmid contains a gene expression cassette inserted in the E1 deleted region, an origin of replication, a selectable marker, and the recombinant adenovirus region is made up of:

a) a first adenovirus region from about base pair 1 to about base 450 corresponding to either Ad5 or Ad6;

b) a gene expression cassette in a E1 parallel or E1 anti-parallel orientation joined to the first region;

c) a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to the expression cassette;

d) a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6, joined to the second region;

e) a fourth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, joined to the third region;

f) a fifth adenovirus region from about base pair 33967 to about base pair 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6, joined to the fourth region, and

g) an optionally present E3 region corresponding to all or part of the E3 region present in Ad5 or Ad6, which may be present for smaller inserts taking into account the overall size of the desired adenovector.

In another embodiment of the present invention the recombinant adenovirus genome plasmid has the gene expression cassette inserted in the E3 deleted region. The vector contains an origin of replication, a selectable marker, and the following:

a) a first adenovirus region from about base pair 1 to about base pair 450 corresponding to either Ad5 or Ad6;

b) a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to the expression cassette;

c) a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6, joined to the second region;

d) the gene expression cassette in a E3 parallel or E3 anti-parallel orientation joined to the third region;

e) a fourth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, joined to the gene expression cassette; and

f) a fifth adenovirus region from about base pair 33967 to about base pair 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6, joined to the fourth region.

In different embodiments concerning adenovirus regions that are present: (1) the first, second, third, fourth, and fifth region corresponds to Ad5; (2) the first, second, third, fourth, and fifth region corresponds to Ad6; and (3) the first region corresponds to Ad5, the second region corresponds to Ad5, the third region corresponds to Ad6, the fourth region corresponds to Ad6, and the fifth region corresponds to Ad5.

An embodiment of the present invention describes a method of making an adenovector involving a homologous recombination step to produce a adenovirus genome plasmid and an adenovirus rescue step. The homologous recombination step involves the use of a shuttle vector containing a Met-NS3-NS4A-NS4B-NS5A-NS5B expression cassette flanked by adenovirus homology regions. The adenovirus homology regions target the expression cassette into either the E1 or E3 deleted region.

In an embodiment of the present invention concerning the production of an adenovirus genome plasmid, the gene expression cassette is inserted into a vector comprising: a first adenovirus region from about base pair 1 to about base pair 450 corresponding to either Ad5 or Ad6; a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to the second region; a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6,

joined to the second region; a fourth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, joined to the third region; and a fifth adenovirus region from about 33967 to about 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6, joined to the fourth region. The adenovirus genome plasmid should contain an origin of replication and a selectable marker, and may contain all or part of the Ad5 or Ad6 E3 region.

In different embodiments concerning adenovirus regions that are present: (1) the first, second, third, fourth, and fifth region corresponds to Ad5; (2) the first, second, third, fourth, and fifth region corresponds to Ad6; and (3) the first region corresponds to Ad5, the second region corresponds to Ad5, the third region corresponds to Ad6, the fourth region corresponds to Ad6, and the fifth region corresponds to Ad5.

B. Adenovector Rescue

An adenovector can be rescued from a recombinant adenovirus genome plasmid using techniques known in the art or described herein. Examples of techniques for adenovirus rescue well known in the art are provided by Hitt *et al.*, *Methods in Molecular Genetics 7*:13-30, 1995, and Danthinne *et al.*, *Gene Therapy 7*:1707-1714, 2000.

A preferred method of rescuing an adenovector described herein involves boosting adenoviral replication. Boosting adenoviral replication can be performed, for example, by supplying adenoviral functions such as E2 proteins (polymerase, pre-terminal protein and DNA binding protein) as well as E4 orf6 on a separate plasmid. Example 10 *infra*. illustrates the boosting of adenoviral replication to rescue an adenovector containing a codon optimized Met-NS3-NS4A-NS4B-NS5A-NS5B expression cassette.

V. PARTIAL-OPITIMIZED HCV ENCODING SEQUENCES

Partial optimization of HCV polyprotein encoding nucleic acid provides for a lesser amount of codons optimized for expression in a human than complete optimization. The overall objective is to provide the benefits of increased expression due to codon optimization, while facilitating the production of an adenovector containing HCV polyprotein encoding nucleic acid having optimized codons.

Complete optimization of an HCV polyprotein encoding sequence provides the most frequently observed human codon for each amino acid. Complete optimization can be performed using codon frequency tables well known in the art and using programs such as the BACKTRANSLATE program (Wisconsin Package version 10, Genetics Computer Group, GCG, Madison, Wisc.).

Partial optimization can be preformed on an entire HCV polyprotein encoding sequence that is present (*e.g.*, NS3-NS5B), or one or more local regions that are present. In different embodiments the GC content for the entire HCV encoded polyprotein that is present is no greater than at least about 65%; and the GC content for one or more local regions is no greater than about 70%.

Local regions are regions present in HCV encoding nucleic acid, and can vary in size. For example, local regions can be about 60, about 70, about 80, about 90 or about 100 nucleotides in length.

Partial optimization can be achieved by initially constructing an HCV encoding polyprotein sequence to be partially optimized based on a naturally ocurring sequence. Alternatively, an optimized HCV encoding sequence can be used as basis of comparison to produce a partial optimized sequence.

VI. HCV COMBINATION TREATMENT

The HCV Met-NS3-NS4A-NS4B-NS5A-NS5B vaccine can be used by itself to treat a patient, can be used in conjunction with other HCV therapeutics, and can be used with agents targeting other types of diseases. Additional therapeutics include additional therapeutic agents to treat HCV and diseases having a high prevalence in HCV infected persons. Agents targeting other types of disease include vaccines directed against HIV and HBV.

Additional therapeutics for treating HCV include vaccines and non-vaccine agents. (Zein, *Expert Opin. Investig. Drugs 10*:1457-1469, 2001.) Examples of additional HCV vaccines include vaccines designed to elicit an immune response against an HCV core antigen and the HCV E1, E2 or p7 region. Vaccine components can be naturally occurring HCV polypeptides, HCV mimotope polypeptides or nucleic acid encoding such polypeptides.

HCV mimotope polypeptides contain HCV epitopes, but have a different sequence than a naturally occurring HCV antigen. A HCV mimotope can be fused to a naturally occurring HCV antigen. References describing techniques for producing mimotopes in general and describing different HCV mimotopes are

provided in Felici *et al.* U.S. Patent No. 5,994,083 and Nicosia *et al.*, International Application Number WO 99/60132.

VII. PHARMACEUTICAL ADMINISTRATION

HCV vaccines can be formulated and administered to a patient using the guidance provided herein along with techniques well known in the art. Guidelines for pharmaceutical administration in general are provided in, for example, *Modern Vaccinology*, Ed. Kurstak, Plenum Med. Co. 1994; *Remington's Pharmaceutical Sciences 18th Edition*, Ed. Gennaro, Mack Publishing, 1990; and *Modern Pharmaceutics 2nd Edition*, Eds. Banker and Rhodes, Marcel Dekker, Inc., 1990, each of which are hereby incorporated by reference herein.

HCV vaccines can be administered by different routes such intravenous, intraperitoneal, subcutaneous, intramuscular, intradermal, impression through the skin, or nasal. A preferred route is intramuscular.

Intramuscular administration can be preformed using different techniques such as by injection with or without one or more electric pulses. Electric mediated transfer can assist genetic immunization by stimulating both humoral and cellular immune responses.

Vaccine injection can be performed using different techniques, such as by employing a needle or a needless injection system. An example of a needless injection system is a jet injection device. (Donnelly *et al.*, International Publication Number WO 99/52463.)

A. Electrically Mediated Transfer

Electrically mediated transfer or Gene Electro-Transfer (GET) can be performed by delivering suitable electric pulses after nucleic acid injection. (See Mathiesen, International Publication Number WO 98/43702). Plasmid injection and electroporation can be performed using stainless needles. Needles can be used in couples, triplets or more complex patterns. In one configuration the needles are soldered on a printed circuit board that is a mechanical support and connects the needles to the electrical field generator by means of suitable cables.

The electrical stimulus is given in the form of electrical pulses. Pulses can be of different forms (square, sinusoidal, triangular, exponential decay) and different polarity (monopolar of positive or negative polarity, bipolar). Pulses can be delivered either at constant voltage or constant current modality.

Different patterns of electric treatment can be used to introduce nucleic acid vaccines including HCV and other nucleic acid vaccines into a patient. Possible patterns of electric treatment include the following:

Treatment 1: 10 trains of 1000 square bipolar pulses delivered every other second, pulse length 0.2 msec/phase, frequency 1000 Hz, constant voltage mode, 45 Volts/phase, floating current.

Treatment 2: 2 trains of 100 square bipolar pulses delivered every other second, pulse length 2 msec/phase, frequency 100 Hz, constant current mode, 100 mA/phase, floating voltage.

Treatment 3: 2 trains of bipolar pulses at a pulse length of about 2 msec/phase, for a total length of about 3 seconds, where the actual current going through the tissue is fixed at about 50 mA.

Electric pulses are delivered through an electric field generator. A suitable generator can be composed of three independent hardware elements assembled in a common chassis and driven by a portable PC which runs the driving program. The software manages both basic and accessory functions. The elements of the device are: (1) signal generator driven by a microprocessor, (2) power amplifier and (3) digital oscilloscope.

The signal generator delivers signals having arbitrary frequency and shape in a given range under software control. The same software has an interactive editor for the waveform to be delivered. The generator features a digitally controlled current limiting device (a safety feature to control the maximal current output). The power amplifier can amplify the signal generated up to +/- 150 V. The oscilloscope is digital and is able to sample both the voltage and the current being delivered by the amplifier.

B. Pharmaceutical Carriers

Pharmaceutically acceptable carriers facilitate storage and administration of a vaccine to a subject. Examples of pharmaceutically acceptable carriers are described herein. Additional pharmaceutical acceptable carriers are well known in the art.

Pharmaceutically acceptable carriers may contain different components such a buffer, normal saline or phosphate buffered saline, sucrose, salts and polysorbate. An example of a pharmaceutically acceptable carrier is follows: 2.5-10 mM TRIS buffer, preferably about 5 mM TRIS buffer; 25-100 mM NaCl, preferably

about 75 mM NaCl; 2.5-10% sucrose, preferably about 5% sucrose; 0.01 -2 mM $MgCl_2$; and 0.001%-0.01% polysorbate 80 (plant derived). The pH is preferably from about 7.0-9.0, more preferably about 8.0. A specific example of a carrier contains 5 mM TRIS, 75 mM NaCl, 5% sucrose, 1 mM $MgCl_2$, 0.005% polysorbate 80 at pH 8.0.

C. Dosing Regimes

Suitable dosing regimens can be determined taking into account the efficacy of a particular vaccine and factors such as age, weight, sex and medical condition of a patient; the route of administration; the desired effect; and the number of doses. The efficacy of a particular vaccine depends on different factors such as the ability of a particular vaccine to produce polypeptide that is expressed and processed in a cell and presented in the context of MHC class I and II complexes.

HCV encoding nucleic acid administered to a patient can be part of different types of vectors including viral vectors such as adenovector, and DNA plasmid vaccines. In different embodiments concerning administration of a DNA plasmid, about 0.1 to 10 mg of plasmid is administered to a patient, and about 1 to 5 mg of plasmid is administered to a patient. In different embodiments concerning administration of a viral vector, preferably an adenoviral vector, about 10^5 to 10^{11} viral particles are administered to a patient, and about 10^7 to 10^{10} viral particles are administered to a patient.

Viral vector vaccines and DNA plasmid vaccines may be administered alone, or may be part of a prime and boost administration regimen. A mixed modality priming and booster inoculation involves either priming with a DNA vaccine and boosting with viral vector vaccine, or priming with a viral vector vaccine and boosting with a DNA vaccine.

Multiple priming, for example, about to 2-4 or more may be used. The length of time between priming and boost may typically vary from about four months to a year, but other time frames may be used. The use of a priming regimen with a DNA vaccine may be preferred in situations where a person has a pre-existing anti-adenovirus immune response.

In an embodiment of the present invention, 1×10^7 to 1×10^{12} particles and preferably about 1×10^{10} to 1×10^{11} particles of adenovector is administered directly into muscle tissue. Following initial vaccination a boost is performed with an adenovector or DNA vaccine.

In another embodiment of the present invention initial vaccination is performed with a DNA vaccine directly into muscle tissue. Following initial vaccination a boost is performed with an adenovector or DNA vaccine.

Agents such as interleukin-12, GM-CSF, B7-1, B7-2, IP10, Mig-1 can be coadministered to boost the immune response. The agents can be coadministered as proteins or through use of nucleic acid vectors.

D. Heterologous Prime-Boost

Heterologous prime-boost is a mixed modality involving the use of one type of viral vector for priming and another type of viral vector for boosting. The heterologous prime-boost can involve related vectors such as vectors based on different adenovirus serotypes and more distantly related viruses such adenovirus and poxvirus. The use of poxvirus and adenovirus vectors to protect mice against malaria is illustrated by Gilbert *et al.*, *Vaccine* 20:1039-1045, 2002.

Different embodiments concerning priming and boosting involve the following types of vectors expressing desired antigens such as Met-NS3-NS4A-NS4B-NS5A-NS5B: Ad5 vector followed by Ad6 vector; Ad6 vector followed by Ad5 vector; Ad5 vector followed by poxvirus vector; poxvirus vector followed by Ad5 vector; Ad6 vector followed by poxvirus vector; and poxvirus vector followed by Ad6 vector.

The length of time between priming and boosting typically varies from about four months to a year, but other time frames may be used. The minimum time frame should be sufficient to allow for an immunological rest. In an embodiment, this rest is for a period of at least 6 months. Priming may involve multiple priming with one type of vector, such as 2-4 primings.

Expression cassettes present in a poxvirus vector should contain a promoter either native to, or derived from, the poxvirus of interest or another poxvirus member. Different strategies for constructing and employing different types of poxvirus based vectors including those based on vaccinia virus, modified vaccinia virus, avipoxvirus, raccoon poxvirus, modified vaccinia virus Ankara, canarypoxviruses (such as ALVAC), fowlpoxviruses, cowpoxviruses, and NYVAC are well known in the art. (Moss, *Current Topics in Microbiology and Immunology 158*:25-38, 1982; Earl *et al.*, In *Current Protocols in Molecular Biology*, Ausubel *et al.* eds., New York: Greene Publishing Associates & Wiley Interscience; 1991:16.16.1-16.16.7, Child *et al.*, *Virology* 174(2):625-9, 1990; Tartaglia *et al.*,

Virology 188:217-232, 1992; U.S. Patent Nos., 4,603,112, 4,722,848, 4,769,330, 5,110,587, 5,174,993, 5,185,146, 5,266,313, 5,505,941, 5,863,542, and 5,942,235.

E. Adjuvants

HCV vaccines can be formulated with an adjuvant. Adjuvants are particularly useful for DNA plasmid vaccines. Examples of adjuvants are alum, $AlPO_4$, alhydrogel, Lipid-A and derivatives or variants thereof, Freund's incomplete adjuvant, neutral liposomes, liposomes containing the vaccine and cytokines, non-ionic block copolymers, and chemokines.

Non-ionic block polymers containing polyoxyethylene (POE) and polyxylpropylene (POP), such as POE-POP-POE block copolymers may be used as an adjuvant. (Newman *et al., Critical Reviews in Therapeutic Drug Carrier Systems 15*:89-142, 1998.) The immune response of a nucleic acid can be enhanced using a non-ionic block copolymer combined with an anionic surfactant.

A specific example of an adjuvant formulation is one containing CRL-1005 (CytRx Research Laboratories), DNA, and benzylalkonium chloride (BAK). The formulation can be prepared by adding pure polymer to a cold (< 5°C) solution of plasmid DNA in PBS using a positive displacement pipette. The solution is then vortexed to solubilize the polymer. After complete solubilization of the polymer a clear solution is obtained at temperatures below the cloud point of the polymer (~6-7°C). Approximately 4 mM BAK is then added to the DNA/CRL-1005 solution in PBS, by slow addition of a dilute solution of BAK dissolved in PBS. The initial DNA concentration is approximately 6 mg/mL before the addition of polymer and BAK, and the final DNA concentration is about 5 mg/mL. After BAK addition the formulation is vortexed extensively, while the temperature is allowed to increase from ~ 2°C to above the cloud point. The formulation is then placed on ice to decrease the temperature below the cloud point. Then, the formulation is vortexed while the temperature is allowed to increase from ~2°C to above the cloud point. Cooling and mixing while the temperature is allowed to increase from ~2°C to above the cloud point is repeated several times, until the particle size of the formulation is about 200-500 nm, as measured by dynamic light scattering. The formulation is then stored on ice until the solution is clear, then placed in storage at –70°C. Before use, the formulation is allowed to thaw at room temperature.

F. Vaccine Storage

Adenovector and DNA vaccines can be stored using different types of buffers. For example, buffer A105 described in Example 9 *infra.* can be used to for vector storage.

Storage of DNA can be enhanced by removal or chelation of trace metal ions. Reagents such as succinic or malic acid, and chelators can be used to enhance DNA vaccine stability. Examples of chelators include multiple phosphate ligands and EDTA. The inclusion of non-reducing free radical scavengers, such as ethanol or glycerol, can also be useful to prevent damage of DNA plasmid from free radical production. Furthermore, the buffer type, pH, salt concentration, light exposure, as well as the type of sterilization process used to prepare the vials, may be controlled in the formulation to optimize the stability of the DNA vaccine.

VII. EXAMPLES

Examples are provided below to further illustrate different features of the present invention. The examples also illustrate useful methodology for practicing the invention. These examples do not limit the claimed invention.

Example 1: Met-NS3-NS4A-NS4B-NS5A-NS5B Expression Cassettes

Different gene expression cassettes encoding HCV NS3-NS4A-NS4B-NS5A-NS5B were constructed based on a 1b subtype HCV BK strain. The encoded sequences had either (1) an active NS5B sequence ("NS"), (2) an inactive NS5B sequence ("NSmut"), (3) a codon optimized sequence with an inactive NS5B sequence ("NSOPTmut"). The expression cassettes also contained a CMV promoter/enhancer and the BGH polyadenylation signal.

The NS nucleotide sequence (SEQ. ID. NO. 5) differs from HCV BK strain GenBank accession number M58335 by 30 out of 5952 nucleotides. The NS amino acid sequence (SEQ. ID. NO. 6) differs from the corresponding 1b genotype HCV BK strain by 7 out of 1984 amino acids. To allow for initiation of translation an ATG codon is present at the 5' end of the NS sequence. A TGA termination sequence is present at the 3' end of the NS sequence.

The NSmut nucleotide sequence (SEQ. ID. NO. 2, Figure 2), is similar to the NS sequence. The differences between NSmut and NS include NSmut having an altered NS5B catalytic site; an optimal ribosome binding site at the 5' end; and a TAAA termination sequence at the 3' end. The alterations in NS5B comprise bases

5138 to 5146, which encode amino acids 1711 to 1713. The alterations result in a change of amino acids GlyAspAsp into AlaAlaGly and creates an inactive form of the NS5B RNA-dependent RNA-polymerase NS5B.

The NSOPTmut sequence (SEQ. ID. NO. 3, Figure 3) was designed based on the amino acid sequence encoded by NSmut. The NSmut amino acid sequence was back translated into a nucleotide sequence with the GCG (Wisconsin Package version 10, Genetics Computer Group, GCG, Madison, Wisc.) BACKTRANSLATE program. To generate a NSOPTmut nucleotide sequence where each amino acid is coded for by the corresponding most frequently observed human codon, the program was run choosing as parameter the generation of the most probable nucleotide sequence and specifying the codon frequency table of highly expressed human genes (human_high.cod) available within the GCG Package as translation scheme.

Example 2: Generation pV1Jns plasmid with NS, NSmut or NSOPTmut Sequences

pV1Jns plasmids containing either the NS sequence, NSmut sequence or NSOPTmut sequences were generated and characterised as follows:

pV1Jns Plasmid with the NS Sequence

The coding region Met-NS3-NS4A-NS4B-NS5A and the coding region Met-NS3-NS4A-NS4B-NS5A-NS5B from a HCV BK type strain (Tomei *et al., J. Virol. 67*:4017-4026, 1993) were cloned into pcDNA3 plasmid (Invitrogen), generating pcD3-5a and pcD3-5b vectors, respectively. PcD3-5A was digested with Hind III, blunt-ended with Klenow fill-in and subsequently digested with Xba I, to generate a fragment corresponding to the coding region of Met-NS3-NS4A-NS4B-NS5A. The fragment was cloned into pV1Jns-poly, digested with Bgl II blunt-ended with Klenow fill-in and subsequently digested with Xba I, generating pV1JnsNS3-5A.

pV1Jns-poly is a derivative of pV1JnsA plasmid (Montgomery et al., *DNA and Cell Biol. 12*:777-783, 1993), modified by insertion of a polylinker containing recognition sites for XbaI, PmeI, PacI into the unique BglII and NotI restriction sites. The pV1Jns plasmid with the NS sequence (pV1JnsNS3-5B) was obtained by homologous recombination into the bacterial strain BJ5183, co-transforming pV1JNS3-5A linearized with XbaI and NotI digestion and a PCR fragment containing approximately 200 bp of NS5A, NS5B coding sequence and

approximately 60 bp of the BGH polyadenylation signal. The resulting plasmid represents pV1Jns-NS.

pV1Jns-NS can be summarized as follows:

Bases	1 to 1881 of pV1JnsA
an additional	AGCTT
then the	Met-NS3-NS5B sequence (SEQ. ID. NO. 5)
then the	wt TGA stop
an additional	TCTAGAGCGTTTAAACCCTTAATTAAGG (SEQ. ID. NO. 14)
Bases	1912 to 4909 of pV1JnsA

pV1Jns Plasmid with the NSmut Sequence

The V1JnsNS3-5A plasmid was modified at the 5' of the NS3 coding sequence by addition of a full Kozak sequence. The plasmid (V1JNS3-5Akozak) was obtained by homologous recombination into the bacterial strain BJ5183, co-transforming V1JNS3-5A linearized by *Afl*II digestion and a PCR fragment containing the proximal part of Intron A, the restriction site BglII, a full Kozak translation initiation sequence and part of the NS3 coding sequence.

The resulting plasmid (V1JNS3-5Akozak) was linearized with Xba I digestion and co-transformed into the bacterial strain BJ5183 with a PCR fragment, containing approximately 200 bp of NS5A, the NS5B mutated sequence, the strong translation termination TAAA and approximately 60 bp of the BGH polyadenylation signal. The PCR fragment was obtained by assembling two 22bp-overlapping fragments where mutations were introduced by the oligonucleotides used for their amplification. The resulting plasmid represents pV1Jns-NSmut.

pV1Jns-NSmut can be summarized as follows:

Bases	1 to 1882 of pV1JnsA
then the	kozak Met-NS3-NS5B(mut) TAAA sequence (SEQ. ID. NO. 2)
an additional	TCTAGA
Bases	1925 to 4909 of pV1JnsA.

pV1Jns Plasmid with the NSOPTmut Sequence

The human codon-optimized synthetic gene (NSOPTmut) with mutated NS5B to abrogate enzymatic activity, full Kozak translation initiation sequence and a strong translation termination was digested with BamHI and SalI

restriction sites present at the 5' and 3' end of the gene. The gene was then cloned into the BglII and SalI restriction sites present in the polylinker of pV1JnsA plasmid, generating pV1Jns-NSOPTmut.

pV1Jns-NSOPTmut can be summarized as follows:

Bases	1 to 1881 of pV1JnsA
an additional	C
then	kozak Met-NS3-NS5B(optmut) TAAA sequence (SEQ. ID. NO. 3)
an additional	TTTAAATGTTTAAAC (SEQ. ID. NO. 15)
Bases	1905 to 4909 of pV1JnsA

Plasmids Characterization

Expression of HCV NS proteins was tested by transfection of HEK 293 cells, grown in 10% FCS/DMEM supplemented by L-glutamine (final 4 mM). Twenty-four hours before transfection, cells were plated in 6-well 35 mm diameter, to reach 90-95% confluence on the day of transfection. Forty nanograms of plasmid DNA (previously assessed as a non-saturating DNA amount) were co-transfected with 100 ng of pRSV-Luc plasmid containing the luciferase reporter gene under the control of Rous sarcoma virus promoter, using the LIPOFECTAMINE 2000 reagent. Cells were kept in a CO_2 incubator for 48 hours at 37 °C.

Cell extracts were prepared in 1% Triton/TEN buffer. The extracts were normalized for Luciferase activity, and run in serial dilution on 10% SDS-acrylamide gel. Proteins were transferred on nitrocellulose and assayed with antibodies directed against NS3, NS5A and NS5B to assess strength of expression and correct proteolytic cleavage. Mock-transfected cells were used as a negative control. Results from representative experiments testing pV1JnsNS, pV1JnsNSmut and pV1JnsNSOPTmut are shown in Figure 12.

Example 3: Mice Immunization with Plasmid DNA Vectors

The DNA plasmids pV1Jns-NS, pV1Jns-NSmut and pV1Jns-NSOPTmut were injected in different mice strains to evaluate their potential to elicit anti-HCV immune responses. Two different strains (Balb/C and C57Black6, N=9-10) were injected intramuscularly with 25 or 50 μg of DNA followed by electrical pluses. Each animal received two doses at three weeks interval.

Humoral immune response elicited in C57Black6 mice against the NS3 protein was measured in post dose two sera by ELISA on bacterially expressed NS3

protease domain. Antibodies specific for the tested antigen were detected in animals immunized with all three vectors with geometric mean titers (GMT) ranging from 94000 to 133000 (Tables 1-3).

Table 1: pV1jns-NS

										GMT
Mice n.	1	2	3	4	5	6	7	8	9	
Titer	105466	891980	78799	39496	543542	182139	32351	95028	67800	94553

Table 2: pV1jns-NSmut

										GMT
Mice n.	11	12	13	14	15	16	17	18	19	20	
Titer	202981	55670	130786	49748	17672	174958	44304	37337	78182	193695	75083

Table 3: pV1jns-NSOPTmut

											GMT
Mice n.	21	22	23	24	25	26	27	28	29	30	
Titer	310349	43645	63496	82174	630778	297259	66861	146735	173506	77732	133165

A T cell response was measured in C57Black6 mice immunized with two intramuscular injections at three weeks interval with 25 μg of plasmid DNA. Quantitative ELIspot assay was performed to determine the number of IFNγ secreting T cells in response to five pools of 20mer peptides overlapping by ten residues encompassing the NS3-NS5B sequence. Specific CD8+ response was analyzed by the same assay using a 20mer peptide encompassing a CD8+ epitope for C57Black6 mice (pep1480).

Cells secreting IFNγ in an antigen specific-manner were detected using a standard ELIspot assay. T cell response in C57Black6 mice immunized with two intramuscular injections at three weeks interval with 50 μg of plasmid DNA, was

analyzed by the same ELIspot assay measuring the number of IFNγ secreting T cells in response to five pools of 20mer peptides overlapping by ten residues encompassing the NS3-NS5B sequence.

Spleen cells were prepared from immunized mice and re-suspended in R10 medium (RPMI 1640 supplemented with 10% FCS, 2 mM L-Glutamine, 50 U/ml-50μg/ml Penicillin/Streptomycin, 10 mM Hepes, 50 μM 2-mercapto-ethanol). Multiscreen 96-well Filtration Plates (Millipore, Cat. No. MAIPS4510, Millipore Corporation, 80 Ashby Road Bedford, MA) were coated with purified rat anti-mouse INFγ antibody (PharMingen, Cat. No. 18181D, PharmiMingen, 10975 Torreyana Road, San Diego, California 92121-1111 USA). After overnight incubation, plates were washed with PBS 1X/0.005% Tween and blocked with 250 μl/well of R10 medium.

Splenocytes from immunized mice were prepared and incubated for twenty-four hours in the presence or absence of 10 μM peptide at a density of 2.5 X 10^5/well or 5 X 10^5/well. After extensive washing (PBS 1X/0.005% Tween), biotinylated rat anti-mouse IFNγ antibody (PharMingen, Cat. No. 18112D, PharMingen, 10975 Torreyana Road, San Diego, California 92121-1111 USA) was added and incubated overnight at 4° C. For development, streptavidin-AKP (PharMingen, Cat. No. 13043E, PharMingen, 10975 Torreyana Road, San Diego, California 92121-1111 USA) and 1-Step™ NBT-BCIP development solution (Pierce, Cat. No. 34042, Pierce, P.O. Box 117, Rockford, IL 61105 USA) were added.

Pools of 20mer overlapping peptides encompassing the entire sequence of the HCV BK strain NS3 to NS5B were used to reveal HCV-specific IFNγ-secreting T cells. Similarly a single 20mer peptide encompassing a CD8+ epitope for C57Black6 mice was used to detect CD8 response. Representative data from groups of C57Black6 and Balb/C mice (N=9-10) immunized with two injections of 25 or 50 μg of plasmid vectors pV1Jns-NS, pV1Jns-NSmut and pV1Jns-NSOPTmut are shown in Figures 13A and 13B.

<u>Example 4: Immunization of Rhesus Macaques</u>

Rhesus macaques (N=3) were immunized by intramuscular injection with 5mg of plasmid pV1Jns-NSOPTmut in 7.5mg/ml CRL1005, Benzalkonium chloride 0.6 mM. Each animal received two doses in the deltoid muscle at 0, and 4 weeks.

CMI was measured at different time points by IFN-γ ELISPOT. This assay measures HCV antigen-specific CD8+ and CD4+ T lymphocyte responses, and can be used for a variety of mammals, such as humans, rhesus monkeys, mice, and rats.

The use of a specific peptide or a pool of peptides can simplify antigen presentation in CTL cytotoxicity assays, interferon-gamma ELISPOT assays and interferon-gamma intracellular staining assays. Peptides based on the amino acid sequence of various HCV proteins (core, E2, NS3, NS4A, NS4B, NS5A, NS5B) were prepared for use in these assays to measure immune responses in HCV DNA and adenovirus vector vaccinated rhesus monkeys, as well as in HCV-infected humans. The individual peptides are overlapping 20-mers, offset by 10 amino acids. Large pools of peptides can be used to detect an overall response to HCV proteins while smaller pools and individual peptides may be used to define the epitope specificity of a response.

IFNγ ELISPOT

The IFNγ-ELISPOT assay provides a quantitative determination of HCV-specific T lymphocyte responses. PBMC are serially diluted and placed in microplate wells coated with anti-rhesus IFN-γ antibody (MD-1 U-Cytech). They are cultured with a HCV peptide pool for 20 hours, resulting in the restimulation of the precursor cells and secretion of IFN-γ. The cells are washed away, leaving the secreted IFN bound to the antibody-coated wells in concentrated areas where the cells were sitting. The captured IFN is detected with biotinylated anti-rhesus IFN antibody (detector Ab U-Cytech) followed by alkaline phosphatase-conjugated streptavidin (Pharmingen 13043E). The addition of insoluble alkaline phosphatase substrate results in dark spots in the wells at the sites where the cells were located, leaving one spot for each T cell that secreted IFN-γ.

The number of spots per well is directly related to the precursor frequency of antigen-specific T cells. Gamma interferon was selected as the cytokine visualized in this assay (using species specific anti-gamma interferon monoclonal antibodies) because it is the most common, and one of the most abundant cytokines synthesized and secreted by activated T lymphocytes. For this assay, the number of spot forming cells (SFC) per million PBMCs is determined for samples in the

presence and absence (media control) of peptide antigens. Data from Rhesus macaques on PBMC from post dose two material are shown in Table 4.

Table 4

	PV1J-NSOPTmut		
Pep pools	21G	99C161	99C166
F (NS3p)	8	10	170
G (NS3h)	7	592	229
H (NS4)	3	14	16
I (NS5a)	5	71	36
L (NS5b)	14	23	11
M (NS5b)	3	35	8
DMSO	2	4	5

INFγELISPOT on PBMC from Rhesus monkeys immunized with two injections of 5 mg DNA/dose in OPTIVAX/BAK of plasmid pV1Jns-NSOPTmut. Data are expressed as SFC7 10^6 PBMC.

Example 5: Construction of Ad6 Pre-Adenovirus Plasmids

Ad6 pre-adenovirus plasmids were obtained as follows:

Construction of pAd6 E1-E3+ Pre-adenovirus Plasmid

An Ad6 based pre-adenovirus plasmid which can be used to generate first generation Ad6 vectors was constructed either taking advantage of the extensive sequence identity (approx. 98%) between Ad5 and Ad6 or containing only Ad6 regions. Homologous recombination was used to clone wtAd6 sequences into a bacterial plasmid.

A general strategy used to recover pAd6E1-E3+ as a bacterial plasmid containing Ad5 and Ad6 regions is illustrated in Figure 10. Cotransformation of BJ 5183 bacteria with purified wt Ad6 viral DNA and a second DNA fragment termed the Ad5 ITR cassette resulted in the circularization of the viral genome by homologous recombination. The ITR cassette contains sequences from the right (bp 33798 to 35935) and left (bp 1 to 341 and bp 3525 to 5767) end of the Ad5 genome separated by plasmid sequences containing a bacterial origin of replication and an ampicillin resistance gene. The ITR cassette contains a deletion of E1 sequences from

Ad5 342 to 3524. The Ad5 sequences in the ITR cassette provide regions of homology with the purified Ad6 viral DNA in which recombination can occur.

Potential clones were screened by restriction analysis and one clone was selected as pAd6E1-E3+. This clone was then sequenced in it entirety. pAd6E1-E3+ contains Ad5 sequences from bp 1 to 341 and from bp 3525 to 5548, Ad6 bp 5542 to 33784, and Ad5 bp 33967 to 35935 (bp numbers refer to the wt sequence for both Ad5 and Ad6). pAd6E1-E3+ contains the coding sequences for all Ad6 virion structural proteins which constitute its serotype specificity.

A general strategy used to recover pAd6E1-E3+ as a bacterial plasmid containing Ad6 regions is illustrated in Figure 11. Cotransformation of BJ 5183 bacteria with purified wt Ad6 viral DNA and a second DNA fragment termed the Ad6 ITR cassette resulted in the circularization of the viral genome by homologous recombination. The ITR cassette contains sequences from the right (bp 35460 to 35759) and left (bp 1 to 450 and bp 3508 to 3807) end of the Ad6 genome separated by plasmid sequences containing a bacterial origin of replication and an ampicillin resistance gene. These three segments were generated by PCR and cloned sequentially into pNEB193, generating pNEBAd6-3 (the ITR cassette). The ITR cassette contains a deletion of E1 sequences from Ad5 451 to 3507. The Ad6 sequences in the ITR cassette provide regions of homology with the purified Ad6 viral DNA in which recombination can occur.

Construction of pAd6 E1-E3- pre-adenovirus plasmids

Ad6 based vectors containing A5 regions and deleted in the E3 region were constructed starting with pAd6E1-E3+ containing Ad5 regions. A 5322 bp subfragment of pAd6E1-E3+ containing the E3 region (Ad6 bp 25871 to 31192) was subcloned into pABS.3 generating pABSAd6E3. Three E3 deletions were then made in this plasmid generating three new plasmids pABSAd6E3(1.8Kb) (deleted for Ad6 bp 28602 to 30440), pABSAd6E3(2.3Kb) (deleted for Ad6 bp 28157 to 30437) and pABSAd6E3(2.6Kb) (deleted for Ad6 bp 28157 to 30788). Bacterial recombination was then used to substitute the three E3 deletions back into pAd6E1-E3+ generating the Ad6 genome plasmids pAd6E1-E3-1.8Kb, pAd6E1-E3-2.3Kb and pAd6E1-E3-2.6Kb.

Example 6: Generation of Ad5 Genome Plasmid with the NS Sequence

A pcDNA3 plasmid (Invitrogen) containing the coding region NS3-NS4A-NS4B-NS5A was digested with *Xmn*I and *Nru*I restriction sites and the DNA fragment containing the CMV promoter, the NS3-NS4A-NS4B-NS5A coding sequence and the Bovine Growth Hormone (BGH) polyadenylation signal was cloned into the unique *Eco*rV restriction site of the shuttle vector pDelE1Spa, generating the Sva3-5A vector.

A pcDNA3 plasmid containing the coding region NS3-NS4A-NS4B-NS5A-NS5B was digested with *Xmn*I and *Eco*rI (partial digestion), and the DNA fragment containing part of NS5A, NS5B gene and the BGH polyadenylation signal was cloned into the Sva3-5A vector, digested *Eco*rI and *Bgl*II blunted with Klenow, generating the Sva3-5B vector.

The Sva3-5B vector was finally digested *Ssp*I and *Bst*1107I restriction sites and the DNA fragment containing the expression cassette (CMV promoter, NS3-NS4A-NS4B-NS5A-NS5B coding sequence and the BGH polyadenylation signal) flanked by adenovirus sequences was co-transformed with pAd5HVO (E1-,E3-) ClaI linearized genome plasmid into the bacterial strain BJ5183, to generate pAd5HVONS. pAd5HVO contains Ad5 bp 1 to 341, bp 3525 to 28133 and bp 30818 to 35935.

Example 7: Generation of Adenovirus Genome Plasmids with the NSmut Sequence

Adenovirus genome plasmids containing an NS-mut sequence were generated in an Ad5 or Ad6 background. The Ad6 background contained Ad5 regions at bases 1 to 450, 3511 to 5548 and 33967 to 35935.

pV1JNS3-5Akozak was digested with *Bgl*II and *Xba*I restriction enzymes and the DNA fragment containing the Kozak sequence and the sequence coding NS3-NS4A-NS4B-NS5A was cloned into a *Bgl*II and XbaI digested polypMRKpdelE1 shuttle vector. The resulting vector was designated shNS3-5Akozak.

PolypMRKpdelE1 is a derivative of RKpdelE1(Pac/pIX/pack450) + CMVmin+BGHpA(str.) modified by the insertion of a polylinker containing recognition sites for BglII, PmeI, SwaI, XbaI, SalI, into the unique BglII restriction site present downstream the CMV promoter. MRKpdelE1(Pac/pIX/pack450) + CMVmin + BGHpA(str.) contains Ad5 sequences from bp 1 to 5792 with a deletion of E1 sequences from bp 451 to 3510. The human CMV promoter and BGH polyadenylation signal were inserted into the E1 deletion in an E1 parallel orientation with a unique BglII site separating them.

The NS5B fragment, mutated to abrogate enzymatic activity and with a strong translation termination at the 3' end, was obtained by assembly PCR and inserted into the shNS3-5Akozak vector via homologous recombination, generating polypMRKpdelE1NSmut. In polypMRKpdelE1NSmut the NS-mut coding sequence is under the control of CMV promoter and the BGH polyadenylation signal is present downstream.

The gene expression cassette and the flanking regions which contain adenovirus sequences allowing homologous recombination were excised by digestion with *Pac*I and *Bst*1107I restriction enzymes and co-transformed with either pAd5HVO (E1-,E3-) or pAd6E1-E3-2.6Kb *Cla*I linearized genome plasmids into the bacterial strain BJ5183, to generate pAd5HVONSmut and pAd6E1-,E3-NSmut, respectively.

pAd6E1-E3-2.6Kb contains Ad5 bp 1 to 341 and from bp 3525 to 5548, Ad6 bp 5542 to 28157 and from bp 30788 to 33784, and Ad5 bp 33967 to 35935 (bp numbers refer to the wt sequence for both Ad5 and Ad6). In both plasmids the viral ITR's are joined by plasmid sequences that contain the bacterial origin of replication and an ampicillin resistance gene.

Example 8: Generation of Adenovirus Genome Plasmids with the NSOPTmut

The human codon-optimized synthetic gene (NSOPTmut) provided by SEQ. ID. NO. 3 cloned into a pCRBlunt vector (Invitrogen) was digested with *BamH*1 and *Sal*I restriction enzymes and cloned into *Bgl*II and *Sal*I restriction sites present in the shuttle vector polypMRKpdelE1. The resulting clone (polypMRKpdelE1NSOPTmut) was digested with *Pac*I and *Bst*1107I restriction enzymes and co-transformed with either pAd5HVO (E1-,E3-) or pAd6E1-E3-2.6Kb *Cla*I linearized genome plasmids, into the bacterial strain BJ5183, to generate pAd5HVONSOPTmut and pAd6E1-,E3-NSOPTmut, respectively.

Example 9: Rescue and Amplification of Adenovirus Vectors

Adenovectors were rescued in Per.6 cells. Per.C6 were grown in 10% FCS / DMEM supplemented by L-glutamine (final 4mM), penicillin/streptomycin (final 100 IU/ml) and 10 mM $MgCl_2$. After infection, cells were kept in the same medium supplemented by 5% horse serum (HS). For viral rescue, 2.5×10^6 Per.C6 were plated in 6 cm ø Petri dishes.

Twenty-four hours after plating, cells were transfected by calcium phosphate method with 10 µg of the *Pac I* linearized adenoviral DNA. The DNA precipitate was left on the cells for 4 hours. The medium was removed and 5% HS/DMEM was added.

Cells were kept in a CO_2 incubator until a cytopathic effect was visible (1 week). Cells and supernatant were recovered and subjected to 3X freeze/thawing cycles (liquid nitrogen / water bath at 37°C). The lysate was centrifuged at 3000 rpm at - 4°C for 20 minutes and the recovered supernatant (corresponding to a cell lysate containing virus passed on cells only once; P1) was used, in the amount of 1 ml/ dish, to infect 80-90% confluent Per.C6 in 10 cm ø Petri dishes. The infected cells were incubated until a cytopathic effect was visible, cells and supernatant recovered and the lysate prepared as described above (P2).

P2 lysate (4 ml) were used to infect 2 X 15 cm ø Petri dishes. The lysate recovered from this infection (P3) was kept in aliquots at –80°C as a stock of virus to be used as starting point for big viral preparations. In this case, 1 ml of the stock was enough to infect 2 X 15 cm ø Petri dishes and resulting lysate (P4) was used for the infection of the Petri dishes devoted to the large scale infection.

Further amplification was obtained from the P4 lysate which was diluted in medium without FCS and used to infect 30 X 15 cm ø Petri dishes (with Per.C6 80%-90% confluent) in the amount of 10 ml/dish. Cells were incubated 1 hour in the CO_2 incubator, mixing gently every 20 minutes. 12 ml / dish of 5% HS / DMEM was added and cells were incubated until a cytopathic effect was visible (about 48 hours).

Cells and supernatant were collected and centrifuged at 2K rpm for 20 minutes at 4°C. The pellet was resuspended in 15 ml of 0.1 M Tris pH=8.0. Cells were lysed by 3X freeze/thawing cycles (liquid nitrogen / water bath at 37°C). 150 µl of 2 M $MgCl_2$ and 75 µl of DNAse (10 mg of bovine pancreatic deoxyribonuclease I in 10 ml of 20 mM Tris-HCl pH= 7.4, 50 mM NaCl, 1 mM dithiothreitol, 0.1 mg/ml bovine serum albumin, 50% glycerol) were added. After a 1 hour incubation at 37°C in a water bath (vortex every 15 minutes) the lysate was centrifuged at 4K rpm for 15 minutes at 4°C. The recovered supernatant was ready to be applied on CsCl gradient.

The CsCl gradients were prepared in SW40 ultra-clear tubes as follows:

0.5 ml of 1.5d CsCl

3 ml of 1.35d CsCl

3 ml of 1.25d CsCl

5-ml/ tube of viral supernatant was applied.

If necessary, the tubes were topped up with 0.1 M tris-Cl pH=8.0. Tubes were centrifuged at 35K rpm for 1 hour at -10^{0}C with rotor SW40. The viral bands (located at the 1.25/1.35 interface) were collected using a syringe.

The virus was transferred into a new SW40 ultraclear tube and 1.35d CsCl was added to top the tube up. After centrifugation at 35K rpm for 24 hours at 10^{0}C in the rotor SW40, the virus was collected in the smallest possible volume and dialyzed extensively against buffer A105 (5 mM Tris, 5% sucrose, 75 mM NaCl, 1 mM $MgCl_2$, 0.005% polysorbate 80 pH=8.0). After dialysis, glycerol was added to final 10% and the virus was stored in aliquots at – 80^{0}C.

Example 10: Enhanced Adenovector Rescue

First generation Ad5 and Ad6 vectors carrying HCV NSOPTmut transgene were found to be difficult to rescue. A possible block in the rescue process might be attributed to an inefficient replication of plasmid DNA that is a sub-optimal template for the replication machinery of adenovirus. The absence of the terminal protein linked to the 5'ends of the DNA (normally present in the viral DNA), associated with the very high G-C content of the transgene inserted in the E1 region of the vector, may be causing a substantial reduction in replication rate of the plasmid-derived adenovirus.

To set up a more efficient and reproducible procedure for rescuing Ad vectors, an expression vector (pE2; Figure 19) containing all E2 proteins (polymerase, pre-terminal protein and DNA binding protein) as well as E4 orf6 under the control of tet-inducible promoter was employed. The transfection of pE2 in combination with a normal preadeno plasmid in PerC6 and in 293 leads to a strong increase of Ad DNA replication and to a more efficient production of complete infectious adenovirus particles.

Plasmid Construction

pE2 is based on the cloning vector pBI (CLONTECH) with the addition of two elements to allow episomal replication and selection in cell culture: (1) the EBV-OriP (EBV [nt] 7421-8042) region permitting plasmid replication in synchrony with the cell cycle when EBNA-1 is expressed and (2) the hygromycin-B phosphotransferase (HPH)-resistance gene allowing a positive selection of

transformed cells. The two transcriptional units for the adenoviral genes E2 a and b and E4-Orf6 were constructed and assembled in pE2 as described below.

The Ad5-Polymerase *ClaI/SphI* fragment and the Ad5-pTP *Acc65/EcoRV* fragment were obtained from pVac-Pol and pVac-pTP (Stunnenberg *et al. NAR 16*:2431-2444, 1988). Both fragments were filled with Klenow and cloned into the *SalI* (filled) and *EcoRV* sites of pBI, respectively obtaining pBI-Pol/pTP.

EBV-OriP element from pCEP4 (Invitrogen) was first inserted within two chicken β-globin insulator dimers by cloning it into *BamHI* site of pJC13-1 (Chung *et al., Cell 74(3)*:505-14, 1993). HS4-OriP fragment from pJC13-OriP was then cloned inside pSA1mv (a plasmid containing tk-Hygro-B resistance gene expression cassette as well as Ad5 replication origin), the ITR's arranged as head-to-tail junction, obtained by PCR from pFG140 (Graham, *EMBO J. 3*:2917-2922, 1984) using the following primers: 5'-TCGAATCGATACGCGAACCTACGC-3' (SEQ. ID. NO. 16) and 5'-TCGACGTGTCGACTTCGAAGCGCACACCAAAAACGTC-3' (SEQ. ID. NO. 17), thus generating pMVHS4Orip. A DNA fragment from pMVHS4Orip, containing the insulated OriP, Ad5 ITR junction and tk-HygroB cassette, was then inserted into pBI-Pol/pTP vector restricted *AseI/AatII* generating pBI-Pol/pTPHS4 .

To construct the second transcriptional unit expressing Ad5-Orf6 as well as Ad5-DBP, E4orf6 (Ad 5 [nt] 33193-34077) obtained by PCR was first inserted into pBI vector, generating pBI-Orf6. Subsequently, DBP coding DNA sequence (Ad 5 [nt] 22443-24032) was inserted into pBI-Orf6 obtaining the second bi-directional Tet-regulated expression vector (pBI-DBP/E4orf6). The original polyA signals present in pBI were substituted with BGH and SV40 polyA.

pBI-DBP/E4orf6 was then modified by inserting a DNA fragment containing the Adeno5-ITRs arranged in head-to-tail junction plus the hygromicin B resistance gene obtained from plasmid pSA-1mv. The new plasmid pBI-DBP/E4orf6shuttle was then used as donor plasmid to insert the second tet-regulated transcriptional unit into pBI-Pol/pTPHS4 by homologous recombination using *E. coli* strain BJ5183 obtaining pE2.

Cell lines, Transfections and Virus Amplification

PerC6 cells were cultured in Dulbecco's modified Eagle's Medium (DMEM) plus 10% fetal bovine serum (FBS), 10 mM $MgCl_2$, penicillin (100 U/ml), streptomycin (100 μg/ml) and 2 mM glutamine.

All transient transfections were performed using Lipofectamine2000 (Invitrogen) as described by the manufacturer. 90% confluent PERC.6™ planted in 6-cm plates were transfected with 3.5 μg of Ad5/6NSOPTmut pre-adeno plasmids, digested with PacI, alone or in combination with 5 μg pE2 plus 1 μg pUHD52.1. pUHD52.1 is the expression vector for the reverse tet transactivator 2 (rtTA2) (Urlinger *et al.*, *Proc. Natl. Acad. Sci. U.S.A. 97(14)*:7963-7968, 2000). Upon transfection, cells were cultivated in the presence of 1 μg/ml of doxycycline to activate pE2 expression. 7 days post-transfection cells were harvested and cell lysate was obtained by three cycles of freeze-thaw. Two ml of cell lysate were used to infect a second 6-cm dish of PerC6. Infected cells were cultivated until a full CPE was observed then harvested. The virus was serially passaged five times as described above, then purified on CsCl gradient. The DNA structure of the purified virus was controlled by endonuclease digestion and agarose gel electrophoresis analysis and compared to the original pre-adeno plasmid restriction pattern.

Example 11: Partial Optimizeation of HCV Polyprotein Encoding Nucleic acid

Partial optimization of HCV polyprotein encoding nucleic acid was performed to facilitate the production of adenovectors containing codons optimized for expression in a human host. The overall objective was to provide for increased expression due to codon optimization, while facilitating the production of an adenovector encoding HCV polyprotein.

Several difficulties were encountered in producing an adenovector encoding HCV polyprotein with codons optimized for expression in a human host. An adenovector containing an optimized sequence (SEQ. ID. NO. 3) was found to be more difficult to synthesize and rescue than an adenovector containing a non-optimized sequence (SEQ. ID. NO. 2).

The difficulties in producing an adenovector containing SEQ. ID. NO. 3 were attributed to a high GC content. A particularly problemetic region was the region at about position 3900 of NSOPTmut (SEQ. ID. NO. 3).

Alternative versions of optimized HCV encoding nucleic acid sequence were designed to facilitate its use in an adenovector. The alternative versions, compared to NSOPTmut, were designed to have a lower overall GC content, to reduce/avoid the presence of potentially problematic motifis of consecutive G's or C's, while maintaining a high level of codon optimization to allow improved expression of the encoded polyprotein and the individual cleavage products.

A starting point for the generation of a suboptimally codon-optimized sequence is the coding region of the NSOPTmut nucleotide sequence (bases 7 to 5961 of SEQ. ID. NO. 3). Values for codon usage frequencies (normalized to a total of 1.0 for each amino acid) were taken from the file human_high.cod available in the Wisconsin Package Version 10.3 (Accelrys Inc., a wholly owned subsidiary of Pharmacopeia, Inc).

To reduce the local and overall GC content a table defining preferred codon substitutions for each amino acid was manually generated. For each amino acid the codon having 1) a lower GC content as compared to the most frequent codon and 2) a relativly high observed codon usage frequency (as defined in human_high.cod) was choosen as the replacement codon. For example for Arg the codon with the highest frequency is CGC. Out of the other five alternative codons encoding Arg (CGG, AGG, AGA, CGT, CGA) three (AGG, CGT, CGA) reduce the GC content by 1 base, one (AGA) by two bases and one (CGG) by 0 bases. Since the AGA codon is listed in human_high.cod as having a relatively low usage frequency (0.1), the codon substituting CGC was therefore choosen to be AGG with a relative frequency of 0.18. Similar criteria were applied in order to establish codon replacements for the other amino acids resulting in the list shown in Table 5. Parameters applied in the following optimization procedure were determined empirically such that the resulting sequence maintained a considerably improved codon usage (for each amino acid) and the GC content (overall and in form of local stretches of consecutive G's and/or C's) was decreased.

Two examples of partial optimized HCV encoding sequences are provided by SEQ. ID. NO. 10 and SEQ. ID. NO. 11. SEQ. ID. NO. 10 provides a HCV encoding sequence that is partially optimized throughout. SEQ. ID. NO. 11 provides an HCV encoding sequence fully optimized for codon usage with the exception of a region that was partially optimized.

Codon optimization was performed using the following procedure:

Step 1) The coding region of the input fully optimized NSOPTmut sequence was analyzed using a sliding window of 3 codons (9 bases) shifting the window by one codon after each cycle. Whenever a stretch containing 5 or more consecutive C's and/or G's was detected in the window the following replacement rule was applied: Let N indicate the number of codon replacements previously performed. If N is odd replace the middle codon in the window with the codon specified in Table 5, if N is even replace the third terminal codon in the window with the codon

specified in a codon optimization table such as human_high.cod. If Leu or Val is present at the second or third codon do not apply any replacement in order not to introduce Leu or Val codons with very low relative codon usage frequency (see, for example, human_high.cod). In the following cycle analysis of the shifted window was then applied to a sequence containing the replacements of the previous cycle.

The alternating replacement of the middle and terminal codon in the 3 codon window was found empirically to give a more satisfying overall maintenance of optimized codon usage while also reducing GC content (as judged from the final sequence after the procedure). In general, however, the precise replacement strategy depends on the amino acid sequence encoded by the nucelotide sequence under analysis and will have to be determined empirically.

Step 2) The sequence containing all the codon replacements performed during step 1) was then subjected to an additional analysis using a sliding window of 21 codons (63 bases) in length: according to an adjustable parameter the overall GC content in the window was determined. If the GC content in the window was higher than 70% the following codon replacement strategy was applied: In the window replace the codons for the amino acids Asn, Asp, Cys, Glu, His, Ile, Lys, Phe, Tyr by the codons given in Table 5. Restriction of the replacement to this set of amino acids was motivated by the fact that a) the replacement codon still has an accetably high frequency of usage in human_high.cod and b) the average overall human codon usage in CUTG for the replacement codon is nearly as high as the most frequent codon. In the following cycle analysis of the shifted window is then applied to a sequence containing the replacements of the previous cycle.

The threshold 70% was determined empirically by compromising between an overall reduction in GC content and maintenance of a high codon optimization for the individual amino acids. As in step 1) the precise replacement strategy (choice of amino acids and GC content threshold value) will again depend on the amino acid sequence encoded by the nucleotide sequence under analysis and will have to be determined empirically.

Step 3) The sequence generated by steps 1) and 2) was then manually edited and additional codons were changed according to the following criteria: Regions still having a GC content higher than 70% over a window of 21 codons were examined manually and a few codons were replaced again following the scheme given in Table 5.

Subsequent steps were performed to provide for useful restriction sites, remove possible open reading frames on the complementary strand, to add homologous recombinant regions, to add a Kozac signal, and to add a terminator. These steps are numbered 4-7

Step 4) The sequence generated in step 3 was examined for the absence of certain restriction sites (BglII, PmeI and XbaI) and presence of only 1 StuI site to allow a subsequent cloning strategy using a subset of restriction enzymes. Two sites (one for BglII and one for StuI) were removed from the sequence by replacing codons that were part of the respective recognition sites.

Step 5) The sequence generated by steps 1) through 4) was then modified according to allow subsequent generation of a modified NSOPTmut sequence (by homologous recombination). In the sequence obtained from steps 1) through 4) the segment comprising base 3556 to 3755 and the segment comprising base 4456 to 4656 were replaced by the corresponding segments from NSOPTmut. The segment comprising bases 3556 to 4656 of SEQ. ID. NO. 10 can be used to replace the problematic region in NSOPTmut (around position 3900) by homologous recombination thus creating the variant of NSOPTmut having the sequence of SEQ. ID. NO. 11.

Step 6) Analysis of the sequence generated through steps 1) to 5) revealed a potential open reading frame spanning nearly the complete fragment on the complementary strand. Removal of all codons CTA and TTA (Leu) and TCA (Ser) from the sense strand effectively removed all stop codons in one of the reading frames on the complementary strand. Although the likelyhood for transcription of this complementary strand open reading frame and subsequent translation into protein is very small, in order to exclude a potential interference with the transcription and subsequent translation of the sequence encoded on the sense strand, TCA codons for Ser were introduced on the sense approximately every 500 bases. No changes were introduced in the segments introduced during step 5) to allow homologous recombination. The TCA codon for Ser was preferred over the CTA and TTA codons for Leu because of the higher relative frequency for TCA (0.05) as compared to CTA (0.02) and TTA (0.03) in human_high.cod. In addition, the average human codon usage from CUTG favored TCA (0.14 against 0.07 for CTA and TTA).

Step 7) In a final step GCCACC was added at the 5' end of the sequence to generate an optimized internal ribosome entry site (Kozak signal) and a TAAA stop sgnal was added at the 3'. To maintain the initiation of translation

properties of NSsuboptmut the first 8 codons of the coding region were kept identical to the NSOPTmut sequence. The resulting sequence was again checked for the absence of BglII, PmeI and XbaI recognition sites and the presence of only 1 StuI site.

The NSsuboptmut sequence (SEQ. ID. NO. 10) has an overall reduced GC content (63.5%) as compared to NSOPTmut (70.3%) and maintains a well optimized level of codon usage optimization. Nucleotide sequence identity of NSsuboptmut is 77.2% with respect to NSmut.

Table 5: Definition of codon replacements performed during steps 1) and 2).

Amino Acid	Most frequent codon	Relative frequency	Reduction in GC content (bases)	Replacement codon	Relative frequency
Amino Acids where the replacement codon reduces the codon GC-content by 1 base					
Ala	GCC	0.51	1	GCT	0.17
Arg	CGC	0.37	1	AGG	0.18
Asn	AAC	0.78	1	AAT	0.22
Asp	GAC	0.75	1	GAT	0.25
Cys	TGC	0.68	1	TGT	0.32
Glu	GAG	0.75	1	GAA	0.25
Gln	CAG	0.88	1	CAA	0.12
Gly	GGC	0.50	1	GGA	0.14
His	CAC	0.79	1	CAT	0.21
Ile	ATC	0.77	1	ATT	0.18
Lys	AAG	0.82	1	AAA	0.18
Phe	TTC	0.80	1	TTT	0.20
Pro	CCC	0.48	1	CCT	0.19
Ser	AGC	0.34	1	TCT	0.13
Thr	ACC	0.51	1	ACA	0.14
Tyr	TAC	0.74	1	TAT	0.26
Amino Acids with no alternative codon					
Met	ATG	1.00	0	ATG	1.00
Trp	TGG	1.00	0	TGG	1.00

Amino Acids where the replacement codon has a very low relative frequency. These amino acids were excluded from the replacement procedure					
Leu	CTG	0.58	1	TTG	0.06
Val	GTG	0.64	1	GTT	0.07

Example 12: Virus Characterization

Adenovectors were characterized by: (a) measuring the physical particles/ml; (b) running a TaqMan PCR assay; and (c) checking protein expression after infection of HeLa cells.

a) Physical Particles Determination

CsCl purified virus was diluted 1/10 and 1/100 in 0.1% SDS PBS. As a control, buffer A105 was used. These dilutions were incubated 10 minutes at 55°C. After spinning the tubes briefly, O.D. at 260 nm was measured. The amount of viral particles was calculated as follows: 1 OD 260 nm = 1.1 X 10^{12} physical particles/ml. The results were typically between 5 X 10^{11} and 1 X 10^{12} physical particles /ml.

b) TaqMan PCR Assay

TaqMan PCR assay was used for adenovectors genome quantification (Q-PCR particles/ml). TaqMan PCR assay was performed using the ABI Prism 7700-sequence detector. The reaction was performed in a final 50 μl volume in the presence of oligonucleotides (at final 200 nM) and probe (at final 200 μM) specific for the adenoviral backbone. The virus was diluted 1/10 in 0.1% SDS PBS and incubated 10 minutes at 55°C. After spinning the tube briefly, serial 1/10 dilutions (in water) were prepared. 10 μl the 10^{-3}, 10^{-5} and 10^{-7} dilutions were used as templates in the PCR assay.

The amount of particles present in each sample was calculated on the basis of a standard curve run in the same experiment. Typically results were between 1 X 10^{12} and 3 X 10^{12} Q-PCR particles /ml.

c) Expression of HCV Non-Structural Proteins

Expression of HCV NS proteins was tested by infection of HeLa cells. Cells were plated the day before the infection at 1.5 X 10^{6} cells/dish (10 cm ø Petri dishes). Different amounts of CsCl purified virus corresponding to m.o.i. of 50, 250

and 1250 pp/cell were diluted in medium (FCS free) up to a final volume of 5 ml. The diluted virus was added on the cells and incubated for 1 hour at 37°C in a CO_2 incubator (gently mixing every 20 minutes). 5 ml of 5% HS-DMEM was added and the cells were incubated at 37°C for 48 hours.

Cell extracts were prepared in 1% Triton/TEN buffer. The extracts were run on 10% SDS-acrylamide gel, blotted on nitrocellulose and assayed with antibodies directed against NS3, NS5a and NS5b in order to check the correct polyprotein cleavage. Mock-infected cells were used as a negative control. Results from representative experiments testing the Ad5-NS, MRKAd5-NSmut, MRKAd6-NSmut and MRKAd6-NSOPTmut are shown in Figure 14.

Example 13: Mice Immunization with Adenovectors Encoding Different NS Cassettes

The adenovectors Ad5-NS, MRKAd5-NSmut, MRKAd6-NSmut and MRKAd6-NSOPTmut were injected in C57Black6 mice strains to evaluate their potential to elicit anti-HCV immune responses. Groups of animals (N=9-10) were injected intramuscularly with 10^9 pp of CsCl purified virus. Each animal received two doses at three weeks interval.

Humoral immune response against the NS3 protein was measured in post dose two sera from C57Black6 immunized mice by ELISA on bacterially expressed NS3 protease domain. Antibodies specific for the tested antigen were detected with geometric mean titers (GMT) ranging from 100 to 46000 (Tables 6, 7, 8 and 9).

Table 6: Ad5-NS

											GMT
Mice n.	1	2	3	4	5	6	7	8	9	10	
Titer	50	253	50	50	50	2257	504	50	50	50	108

Table 7: Ad5-NSmut

											GMT
Mice n.	11	12	13	14	15	16	17	18	19	20	
Titer	3162	78850	87241	6796	12134	3340	18473	13093	76167	49593	23645

Table 8: MRKAd6-NSmut

											GMT
Mice n.	21	22	23	24	25	26	27	28	29	30	
Titer	125626	39751	40187	65834	60619	69933	21555	49348	29290	26859	46461

Table 9: MRKAd6-NSOPTmut

								GMT
Mice n.	31	32	33	34	35	36	37	
Titer	25430	3657	893	175	10442	49540	173	2785

T cell response in C57Black6 mice was analyzed by the quantitative ELISPOT assay measuring the number of IFNγ secreting T cells in response to five pools (named from F to L+M) of 20mer peptides overlapping by ten residues encompassing the NS3-NS5B sequence. Specific CD8+ response induced in C57Black6 mice was analyzed by the same assay using a 20mer peptide encompassing a CD8+ epitope for C57Black6 mice (pep1480). Cells secreting IFNγ in an antigen specific-manner were detected using a standard ELIspot assay.

Spleen cells, splenocytes and peptides were produced and treated as described in Example 3, *supra*. Representative data from groups of C57Black6 mice (N=9-10) immunized with two injections of 10^9 viral particles of vectors Ad5-NS, MRKAd5-NSmut and MRKAd6-NSmut are shown in Figure 15.

Example 14: Immunization of Rhesus macaques with Adenovectors

Rhesus macaques (N=3-4) were immunized by intramuscular injection of CsCl purified Ad5-NS, MRKAd5-NSmut, MRKAd6-NSmut or MRKAd6-

NSOPTmut virus. Each animal received two doses of 10^{11} or 10^{10} vp in the deltoid muscle at 0, and 4 weeks.

CMI was measured at different time points by a) IFN-γ ELISPOT (see Example 3, *supra*), b) IFN-γ ICS and c) bulk CTL assays. These assays measure HCV antigen-specific CD8+ and CD4+ T lymphocyte responses, and can be used for a variety of mammals, such as humans, rhesus monkeys, mice, and rats.

The use of a specific peptide or a pool of peptides can simplify antigen presentation in CTL cytotoxicity assays, interferon-gamma ELISPOT assays and interferon-gamma intracellular staining assays. Peptides based on the amino acid sequence of various HCV proteins (core, E2, NS3, NS4A, NS4B, NS5a, NS5b) were prepared for use in these assays to measure immune responses in HCV DNA and adenovirus vector vaccinated rhesus monkeys, as well as in HCV-infected humans. The individual peptides are overlapping 20-mers, offset by 10 amino acids. Large pools of peptides can be used to detect an overall response to HCV proteins while smaller pools and individual peptides may be used to define the epitope specificity of a response.

IFN-γ ICS

For IFN-γ ICS, 2 x 10^6 PBMC in 1 ml R10 (RPMI medium, supplemented with 10% FCS) were stimulated with peptide pool antigens. Final concentration of each peptide was 2 μg/ml. Cells were incubated for 1 hour in a CO_2 incubator at 37°C and then Brefeldin A was added to a final concentration of 10 μg /ml to inhibit the secretion of soluble cytokines. Cells were incubated for additional 14-16 hours at 37°C.

Stimulation was done in the presence of co-stimulatory antibodies: CD28 and CD49d (anti-humanCD28 BD340975 and anti-humanCD49d BD340976). After incubation, cells were stained with fluorochrome-conjugated antibodies for surface antigens: anti-CD3, anti-CD4, anti-CD8 (CD3-APC Biosource APS0301, CD4-PE BD345769, CD8-PerCP BD345774).

To detect intracellular cytokines, cells were treated with FACS permeabilization buffer 2 (BD340973), 2x final concentration. Once fixed and permeabilized, cells were incubated with an antibody against human IFN-γ, IFN-γFITC (Biosource AHC4338).

Cells were resuspended in 1% formaldehyde in PBS and analyzed at FACS within 24 hours. Four color FACS analysis was performed on a FACSCalibur

instrument (Becton Dickinson) equipped with two lasers. Acquisition was done gating on the lymphocyte population in the Forward versus Side Scatter plot coupled with the CD3, CD8 positive populations. At least 30,000 events of the gate were taken. The positive cells are expressed as number of IFN-γ expressing cells over 10^6 lymphocytes.

IFN-γ ELISPOT and IFN-γ ICS data from immunized monkeys after one or two injections of 10^{10} or 10^{11} vp of the different adenovectors are reported in Figures 16A-16D, 17A, and 17B.

Bulk CTL Assays

A distinguishing effector function of T lymphocytes is the ability of subsets of this cell population to directly lyse cells exhibiting appropriate MHC-associated antigenic peptides. This cytotoxic activity is most often associated with CD8+ T lymphocytes.

PBMC samples were infected with recombinant vaccine viruses expressing HCV antigens *in vitro* for approximately 14 days to provide antigen restimulation and expansion of memory T cells. Cytotoxicity against autologous B cell lines treated with peptide antigen pools was tested.

The lytic function of the culture is measured as a percentage of specific lysis resulted from chromium released from target cells during 4 hours incubation with CTL effector cells. Specific cytotoxicity is measured and compared to irrelevant antigen or excipient-treated B cell lines. This assay is semi-quantitative and is the preferred means for determining whether CTL responses were elicited by the vaccine. Data after two injections from monkeys immunized with 10^{11} vp/dose with adenovectors Ad5-NS, MRKAd5-NSmut and MRKAd6-NSmut are reported in Figures 18A-18F.

Other embodiments are within the following claims. While several embodiments have been shown and described, various modifications may be made without departing from the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A nucleic acid comprising a nucleotide sequence encoding a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide substantially similar to SEQ ID NO: 1, provided that said polypeptide has sufficient protease activity to process itself to produce an NS5B protein and said NS5B protein is enzymatically inactive.

2. The nucleic acid of claim 1, wherein said nucleotide sequence is substantially similar to the coding sequence of SEQ ID NO: 2.

3. The nucleic acid of claim 1, wherein said nucleotide sequence encodes for the polypeptide of SEQ ID NO: 1.

4. The nucleic acid of claim 3, wherein said nucleotide sequence is the coding sequence of either SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 10, or SEQ ID NO: 11.

5. The nucleic acid of claim 3, wherein said nucleotide sequence is the coding sequence of either SEQ ID NO: 2 or SEQ ID NO: 3.

6. The nucleic acid of any one of claims 1-5, wherein said nucleic acid is an expression vector capable of expressing said polypeptide from said nucleotide sequence in a human cell.

7. A nucleic acid comprising a gene expression cassette able to express a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide substantially similar to SEQ ID NO: 1 in a human cell, provided that said polypeptide can process itself to produce an NS5B protein and said NS5B protein is enzymatically inactive, said expression cassette comprising:

a) a promoter transcriptionally coupled to a nucleotide sequence encoding said polypeptide;

b) a 5' ribosome binding site functionally coupled to said nucleotide sequence,

c) a terminator joined to the 3' end of said nucleotide sequence, and

d) a 3' polyadenylation signal functionally coupled to said nucleotide sequence.

8. The nucleic acid of claim 7, wherein said nucleotide sequence is substantially similar to either SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 10, or SEQ ID NO: 11.

9. The nucleic acid of claim 8, wherein said nucleic acid is a shuttle vector further comprising a selectable marker, an origin of replication, a first adenovirus homology region and a second adenovirus homology region flanking said expression cassette, wherein said first homology region has at least about 100 base pairs substantially homologous to at least right end of a wild-type adenovirus region from about base pairs 1-425, and said second homology region has at least about 100 base pairs substantially homologous to at least the left end of a wild-type adenovirus region from about base pairs 3511-5792 of Ad5 or corresponding region of another adenovirus.

10. The nucleic acid of claim 9, wherein said nucleotide sequence encodes for a polypeptide of SEQ ID NO: 1.

11. The nucleic acid of claim 9, wherein said nucleotide sequence is SEQ ID NO: 2.

12. The nucleic acid of claim 9, wherein said nucleotide sequence is either SEQ ID NO: 3, SEQ ID NO: 10, or SEQ ID NO: 11.

13. The nucleic acid of claim 8, wherein said nucleic acid is a plasmid suitable for administration into a human and further comprises a prokaryotic origin of replication and a gene coding for a selectable marker.

14. The nucleic acid of claim 13, wherein said nucleotide sequence encodes for a polypeptide of SEQ ID NO: 1.

15. The nucleic acid of claim 14, wherein said nucleotide sequence is the coding sequence of either SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 10, or SEQ ID NO: 11.

16. The nucleic acid of claim 14, wherein said nucleotide sequence is the coding sequence of SEQ ID NO: 2 or SEQ ID NO: 3.

17. The nucleic acid of claim 14, wherein said promoter is the human intermediate early cytomegalovirus promoter (intron A), said 5' ribosome binding site consists of SEQ ID NO: 12, and said 3' polyadenylation is the bovine growth hormone (BGH) polyadenylation signal.

18. The nucleic acid of claim 8, wherein said nucleic acid is a adenovirus genome plasmid comprising a selectable marker, an origin of replication, and a recombinant adenovector genome containing an E1 deletion, an E3 deletion, and said expression cassette.

19. The nucleic acid of claim 8, wherein said nucleic acid is a adenovirus genome plasmid comprising a selectable marker, an origin of replication, and

a) a first adenovirus region from about base pair 1 to about base pair 450 corresponding to either Ad5 or Ad6;

b) said gene expression cassette in a E1 parallel or E1 anti-parallel orientation joined to said first region;

c) a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to said expression cassette;

d) a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6, joined to said second region;

e) a fourth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, joined to said third region; and

f) a fifth adenovirus region from about base pair 33967 to about base pair 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6, joined to said fourth region.

20. The nucleic acid of claim 19, wherein said first region corresponds to Ad5, said second region corresponds to Ad5, said third region corresponds to Ad5, said fourth region corresponds to Ad5, and said fifth region corresponds to Ad5.

21. The nucleic acid of claim 20, wherein said promoter is the human intermediate early cytomegalovirus promoter, said 5' ribosome binding site consists of SEQ ID NO: 12, and said 3' polyadenylation is the BGH polyadenylation signal.

22. The nucleic acid of claim 21, wherein said expression cassette is in an E1 anti parallel orientation and said nucleotide sequence is either SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 10, or SEQ ID NO: 11.

23. The nucleic acid of claim 19, wherein said first region corresponds to Ad5 or Ad6, said second region corresponds to Ad5 or Ad6, said third region corresponds to Ad6, said fourth region corresponds to Ad6, and said fifth region corresponds to Ad5 or Ad6.

24. The nucleic acid of claim 23, wherein said promoter is the human intermediate early cytomegalovirus promoter, said 5' ribosome binding site consists of SEQ ID NO: 12, and said 3' polyadenylation is the BGH polyadenylation signal.

25. The nucleic acid of claim 24, wherein said expression cassette is in an E1 anti parallel orientation and said nucleotide sequence is either SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 10, or SEQ ID NO: 11.

26. The nucleic acid of claim 24, wherein said expression cassette is in an E1 anti parallel orientation and said nucleotide sequence is either SEQ ID NO: 2 or SEQ ID NO: 3.

27. The nucleic acid of claim 8, wherein said nucleic acid is a adenovirus genome plasmid comprising an origin of replication, a selectable marker, and:

a) a first adenovirus region from about base pair 1 to about base pair 450 corresponding to either Ad5 or Ad6;

b) a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to said first region;

c) a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6, joined to said second region;

d) said gene expression cassette in a E3 parallel or E3 anti-parallel orientation joined to said third region;

e) a fourth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, joined to said gene expression cassette; and

f) a fifth adenovirus region from about base pair 33967 to about base pair 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6, joined to said fourth region.

28. The nucleic acid of claim 27, wherein said first region corresponds to Ad5, said second region corresponds to Ad5, said third region corresponds to Ad5, said fourth region corresponds to Ad5, and said fifth region corresponds to Ad5.

29. The nucleic acid of claim 28, wherein said promoter is the human intermediate early cytomegalovirus promoter, said 5' ribosome binding site consists of SEQ ID NO: 12, and said 3' polyadenylation is the BGH polyadenylation signal.

30. The nucleic acid of claim 27, wherein said first region corresponds to Ad5 or Ad6, said second region corresponds to Ad5 of Ad6, said third region corresponds to Ad6, said fourth region corresponds to Ad6, and said fifth region corresponds to Ad5 or Ad6.

31. The nucleic acid of claim 30, wherein said promoter is the human intermediate early cytomegalovirus promoter, said 5' ribosome binding site consists of SEQ ID NO: 12, and said 3' polyadenylation is the BGH polyadenylation signal.

32. The nucleic acid of claim 8, wherein said nucleic acid is a adenovector consisting of a nucleotide sequence substantially similar to of SEQ ID NO. 4 or a derivative thereof, wherein said derivative thereof has the HCV polyprotein encoding sequence present in SEQ ID NO: 4 replaced with the HCV polyprotein encoding sequence of either SEQ ID NO: 3, SEQ ID NO: 10 or SEQ ID NO: 11.

33. The nucleic acid of claim 8, wherein said nucleic acid is an adenovector having an adenovector genome containing an E1 deletion, an E3 deletion, and said expression cassette

34. The nucleic acid of claim 8, wherein said nucleic acid is an adenovector consisting of:

a) a first adenovirus region from about base pair 1 to about base pair 450 corresponding to either Ad5 or Ad6;

b) said gene expression cassette in a E1 parallel or E1 anti-parallel orientation joined to said first region;

c) a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to said expression cassette;

d) a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6, joined to said second region;

e) a fourth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, joined to said third region; and

f) a fifth adenovirus region from about base pair 33967 to about base pair 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6, joined to said fourth region.

35. The nucleic acid of claim 34, wherein said first region corresponds to Ad5, said second region corresponds to Ad5, said third region corresponds to Ad5, said fourth region corresponds to Ad5, and said fifth region corresponds to Ad5.

36. The nucleic acid of claim 35, wherein said promoter is the human intermediate early cytomegalovirus promoter, said 5' ribosome binding site consists of SEQ ID NO: 12, and said 3' polyadenylation is the BGH polyadenylation signal.

37. The nucleic acid of claim 36, wherein said expression cassette is in an E1 anti parallel orientation and said nucleotide sequence is either SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 10, or SEQ ID NO: 11.

38. The nucleic acid of claim 34, wherein said first region corresponds to Ad5 or Ad6, said second region corresponds to Ad5 or Ad6, said third region corresponds to Ad6, said fourth region corresponds to Ad6, and said fifth region corresponds to Ad5 or Ad6.

39. The nucleic acid of claim 37, where said promoter is the human intermediate early cytomegalovirus promoter, said 5' ribosome binding site consists of SEQ ID NO: 12, and said 3' polyadenylation is the BGH polyadenylation signal.

40. The nucleic acid of claim 39, wherein said expression cassette is in an E1 anti parallel orientation and said nucleotide sequence is SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 10, or SEQ ID NO: 11.

41. The nucleic acid of claim 39, wherein said expression cassette is in an E1 anti parallel orientation and said nucleotide sequence is SEQ ID NO: 2 or SEQ ID NO: 3.

42. The nucleic acid of claim 8, wherein said nucleic acid is an adenovector consisting of:

a) a first adenovirus region from about base pair 1 to about base pair 450 corresponding to either Ad5 or Ad6;

b) a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to said first region;

c) a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6, joined to said second region;

d) said gene expression cassette in a E3 parallel or E3 anti-parallel orientation joined to said third region;

e) a fourth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, joined to said gene expression cassette; and

f) a fifth adenovirus region from about base pair 33967 to about base pair 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6, joined to said fourth region.

43. The nucleic acid of claim 42, wherein said first region corresponds to Ad5, said second region corresponds to Ad5, said third region corresponds to Ad5, said fourth region corresponds to Ad5, and said fifth region corresponds to Ad5.

44. The nucleic acid of claim 42, wherein said first region corresponds to Ad5 or Ad6, said second region corresponds to Ad5 or Ad6, said third region corresponds to Ad6, said fourth region corresponds to Ad6, and said fifth region corresponds to Ad5 or Ad6.

45. An adenovector consisting of the nucleic acid sequence of SEQ ID NO. 4 or a derivative thereof, wherein said derivative thereof has the HCV polyprotein encoding sequence present in SEQ ID NO: 4 replaced with the HCV polyprotein encoding sequence of either SEQ ID NO: 3, SEQ ID NO: 10 or SEQ ID NO: 11.

46. An adenovector produced by a process comprising the steps of:

a) producing an adenovirus genome plasmid by homologous recombination between the shuttle vector of claim 9 and a nucleic acid comprising;

a first adenovirus region from about base pair 1 to about base pair 450 corresponding to either Ad5 or Ad6;

a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to said first region;

a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6, joined to said second region;

a fourth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, joined to said third region; and

a fifth adenovirus region from about base pair 33967 to about base pair 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6, joined to said fourth region; and

b) rescuing said adenovector from said adenovirus plasmid.

47. A cultured recombinant cell comprising the nucleic acid of claim 6.

48. A cultured recombinant cell comprising the nucleic acid of any one of claims 9-46.

49. A method of making an adenovector comprising the steps of:

a) producing an adenovirus genome plasmid comprising a gene expression cassette by homologous recombination between the nucleic acid of claim 9 and a nucleic acid comprising;

a first adenovirus region from about base pair 1 to about base pair 450 corresponding to either Ad5 or Ad6;

a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to said first region;

a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6, joined to said second region;

a fourth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, joined to said third region; and

a fifth adenovirus region from about base pair 33967 to about base pair 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6, joined to the fourth region; and

b) rescuing said recombinant adenovirus from said recombinant adenovirus plasmid.

50. A pharmaceutical composition comprising the nucleic acid of any one of claims 13-17 and 32-46 and pharmaceutically acceptable carrier.

51. A method of treating a patient comprising the step of administering to said patient an effective amount of the nucleic acid of any one of claims 13-17 and 32-46.

52. The method of claim 51, wherein said patient is a human.

53. The method of claim 52, wherein said patient is not infected with HCV.

54. The method of claim 52, wherein said patient is infected with HCV.

55. A recombinant nucleic acid comprising one or more Ad6 regions and a region not present in Ad6, wherein at least one Ad6 region is selected from the group consisting of: E1A, E1B, E2B, E2A, E4, L1, L2, L4, and L5.

56. The recombinant nucleic acid of claim 55, wherein said region not present in Ad6, is an expression cassette coding for a polypeptide not found in Ad6.

57. The recombinant nucleic acid of claim 56, wherein said recombinant nucleic acid is an adenovirus vector defective in at least E1 that is able to replicate when E1 is supplied *in trans*.

58. The recombinant nucleic acid of claim 57, wherein said vector consists of:

a) a first adenovirus region from about base pair 1 to about base pair 450 corresponding to either Ad5 or Ad6;

b) said gene expression cassette in an E1 parallel or E1 anti-parallel orientation joined to said first region;

c) a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to said gene expression cassette;

d) a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6, joined to said second region;

e) an optionally present fourth region from about base pair 28134 to about base pair 30817 corresponding to Ad5, or from about base pair 28157 to about 30789 corresponding to Ad6, joined to said third region;

f) a fifth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, wherein said fifth region is joined to said fourth region if said fourth region is present, or said fifth is joined to said third region if said fourth region is not present; and

g) a sixth adenovirus region from about base pair 33967 to about base pair 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6, joined to said fourth region;

provided that at least one of said second, third, and fifth regions is from Ad6.

59. The recombinant nucleic acid of claim 57, wherein said vector consists of:

a) a first adenovirus region from about base pair 1 to about base pair 450 corresponding to either Ad5 or Ad6;

b) a second adenovirus region from about base pair 3511 to about base pair 5548 corresponding to Ad5 or from about base pair 3508 to about base pair 5541 corresponding to Ad6, joined to said first region;

c) a third adenovirus region from about base pair 5549 to about base pair 28133 corresponding to Ad5 or from about base pair 5542 to about base pair 28156 corresponding to Ad6, joined to said second region;

d) said gene expression cassette in a E3 parallel or E3 anti-parallel orientation joined to said third region;

e) a fourth adenovirus region from about base pair 30818 to about base pair 33966 corresponding to Ad5 or from about base pair 30789 to about base pair 33784 corresponding to Ad6, joined to said gene expression cassette; and

f) a fifth adenovirus region from about base pair 33967 to about base pair 35935 corresponding to Ad5 or from about base pair 33785 to about base pair 35759 corresponding to Ad6, joined to said fourth region;

provided that at least one of said second, third, and fourth regions is from Ad6.

1	MAPITAYSQQ	TRGLLGCIIT	SLTGRDKNQV	EGEVQVVSTA	TQSFLATCVN
51	GVCWTVYHGA	GSKTLAGPKG	PITQMYTNVD	QDLVGWQAPP	GARSLTPCTC
101	GSSDLYLVTR	HADVIPVRRR	GDSRGSLLSP	RPVSYLKGSS	GGPLLCPSGH
151	AVGIFRAAVC	TRGVAKAVDF	VPVESMETTM	RSPVFTDNSS	PPAVPQSFQV
201	AHLHAPTGSG	KSTKVPAAYA	AQGYKVLVLN	PSVAATLGFG	AYMSKAHGID
251	PNIRTGVRTI	TTGAPVTYST	YGKFLADGGC	SGGAYDIIIC	DECHSTDSTT
301	ILGIGTVLDQ	AETAGARLVV	LATATPPGSV	TVPHPNIEEV	ALSNTGEIPF
351	YGKAIPIEAI	RGGRHLIFCH	SKKKCDELAA	KLSGLGINAV	AYYRGLDVSV
401	IPTIGDVVVV	ATDALMTGYT	GDFDSVIDCN	TCVTQTVDFS	LDPTFTIETT
451	TVPQDAVSRS	QRRGRTGRGR	RGIYRFVTPG	ERPSGMFDSS	VLCECYDAGC
501	AWYELTPAET	SVRLRAYLNT	PGLPVCQDHL	EFWESVFTGL	THIDAHFLSQ
551	TKQAGDNFPY	LVAYQATVCA	RAQAPPPSWD	QMWKCLIRLK	PTLHGPTPLL
601	YRLGAVQNEV	TLTHPITKYI	MACMSADLEV	VTSTWVLVGG	VLAALAAYCL
651	TTGSVVIVGR	IILSGRPAIV	PDREFLYQEF	DEMEECASHL	PYIEQGMQLA
701	EQFKQKALGL	LQTATKQAEA	AAPVVESKWR	ALETFWAKHM	WNFISGIQYL
751	AGLSTLPGNP	AIASLMAFTA	SITSPLTTQS	TLLFNILGGW	VAAQLAPPSA
801	ASAFVGAGIA	GAAVGSIGLG	KVLVDILAGY	GAGVAGALVA	FKVMSGEMPS
851	TEDLVNLLPA	ILSPGALVVG	VVCAAILRRH	VGPGEGAVQW	MNRLIAFASR
901	GNHVSPTHYV	PESDAAARVT	QILSSLTITQ	LLKRLHQWIN	EDCSTPCSGS
951	WLRDVWDWIC	TVLTDFKTWL	QSKLLPQLPG	VPFFSCQRGY	KGVWRGDGIM
1001	QTTCPCGAQI	TGHVKNGSMR	IVGPKTCSNT	WHGTFPINAY	TTGPCTPSPA
1051	PNYSRALWRV	AAEEYVEVTR	VGDFHYVTGM	TTDNVKCPCQ	VPAPEFFTEV
1101	DGVRLHRYAP	ACRPLLREEV	TFQVGLNQYL	VGSQLPCEPE	PDVAVLTSML
1151	TDPSHITAET	AKRRLARGSP	PSLASSSASQ	LSAPSLKATC	TTHHVSPDAD
1201	LIEANLLWRQ	EMGGNITRVE	SENKVVVLDS	FDPLRAEEDE	REVSVPAEIL
1251	RKSKKFPAAM	PIWARPDYNP	PLLESWKDPD	YVPPVVHGCP	LPPIKAPPIP
1301	PPRRKRTVVL	TESSVSSALA	ELATKTFGSS	ESSAVDSGTA	TALPDQASDD
1351	GDKGSDVESY	SSMPPLEGEP	GDPDLSDGSW	STVSEEASED	VVCCSMSYTW
1401	TGALITPCAA	EESKLPINAL	SNSLLRHHNM	VYATTSRSAG	LRQKKVTFDR
1451	LQVLDDHYRD	VLKEMKAKAS	TVKAKLLSVE	EACKLTPPHS	AKSKFGYGAK
1501	DVRNLSSKAV	NHIHSVWKDL	LEDTVTPIDT	TIMAKNEVFC	VQPEKGGRKP
1551	ARLIVFPDLG	VRVCEKMALY	DVVSTLPQVV	MGSSYGFQYS	PGQRVEFLVN
1601	TWKSKKNPMG	FSYDTRCFDS	TVTENDIRVE	ESIYQCCDLA	PEARQAIKSL
1651	TERLYIGGPL	TNSKGQNCGY	RRCRASGVLT	TSCGNTLTCY	LKASAACRAA

FIG. 1A

1701	KLQDCTMLVN	AAGLVVICES	AGTQEDAASL	RVFTEAMTRY	SAPPGDPPQP
1751	EYDLELITSC	SSNVSVAHDA	SGKRVYYLTR	DPTTPLARAA	WETARHTPVN
1801	SWLGNIIMYA	PTLWARMILM	THFFSILLAQ	EQLEKALDCQ	IYGACYSIEP
1851	LDLPQIIERL	HGLSAFSLHS	YSPGEINRVA	SCLRKLGVPP	LRVWRHRARS
1901	VRARLLSQGG	RAATCGKYLF	NWAVKTKLKL	TPIPAASQLD	LSGWFVAGYS
1951	GGDIYHSLSR	ARPRWFMLCL	LLLSVGVGIY	LLPNR	

FIG. 1B

1	GCCACCATGG	CGCCCATCAC	GGCCTACTCC	CAACAGACGC	GGGGCCTACT
51	TGGTTGCATC	ATCACTAGCC	TTACAGGCCG	GGACAAGAAC	CAGGTCGAGG
101	GAGAGGTTCA	GGTGGTTTCC	ACCGCAACAC	AATCCTTCCT	GGCGACCTGC
151	GTCAACGGCG	TGTGTTGGAC	CGTTTACCAT	GGTGCTGGCT	CAAAGACCTT
201	AGCCGGCCCA	AAGGGGCCAA	TCACCCAGAT	GTACACTAAT	GTGGACCAGG
251	ACCTCGTCGG	CTGGCAGGCG	CCCCCCGGGG	CGCGTTCCTT	GACACCATGC
301	ACCTGTGGCA	GCTCAGACCT	TTACTTGGTC	ACGAGACATG	CTGACGTCAT
351	TCCGGTGCGC	CGGCGGGGCG	ACAGTAGGGG	GAGCCTGCTC	TCCCCCAGGC
401	CTGTCTCCTA	CTTGAAGGGC	TCTTCGGGTG	GTCCACTGCT	CTGCCCTTCG
451	GGGCACGCTG	TGGGCATCTT	CCGGGCTGCC	GTATGCACCC	GGGGGGTTGC
501	GAAGGCGGTG	GACTTTGTGC	CCGTAGAGTC	CATGGAAACT	ACTATGCGGT
551	CTCCGGTCTT	CACGGACAAC	TCATCCCCCC	CGGCCGTACC	GCAGTCATTT
601	CAAGTGGCCC	ACCTACACGC	TCCCACTGGC	AGCGGCAAGA	GTACTAAAGT
651	GCCGGCTGCA	TATGCAGCCC	AAGGGTACAA	GGTGCTCGTC	CTCAATCCGT
701	CCGTTGCCGC	TACCTTAGGG	TTTGGGGCGT	ATATGTCTAA	GGCACACGGT
751	ATTGACCCCA	ACATCAGAAC	TGGGGTAAGG	ACCATTACCA	CAGGCGCCCC
801	CGTCACATAC	TCTACCTATG	GCAAGTTTCT	TGCCGATGGT	GGTTGCTCTG
851	GGGGCGCTTA	TGACATCATA	ATATGTGATG	AGTGCCATTC	AACTGACTCG
901	ACTACAATCT	TGGGCATCGG	CACAGTCCTG	GACCAAGCGG	AGACGGCTGG
951	AGCGCGGCTT	GTCGTGCTCG	CCACCGCTAC	GCCTCCGGGA	TCGGTCACCG
1001	TGCCACACCC	AAACATCGAG	GAGGTGGCCC	TGTCTAATAC	TGGAGAGATC
1051	CCCTTCTATG	GCAAAGCCAT	CCCCATTGAA	GCCATCAGGG	GGGGAAGGCA
1101	TCTCATTTTC	TGTCATTCCA	AGAAGAAGTG	CGACGAGCTC	GCCGCAAAGC
1151	TGTCAGGCCT	CGGAATCAAC	GCTGTGGCGT	ATTACCGGGG	GCTCGATGTG
1201	TCCGTCATAC	CAACTATCGG	AGACGTCGTT	GTCGTGGCAA	CAGACGCTCT
1251	GATGACGGGC	TATACGGGCG	ACTTTGACTC	AGTGATCGAC	TGTAACACAT
1301	GTGTCACCCA	GACAGTCGAC	TTCAGCTTGG	ATCCCACCTT	CACCATTGAG
1351	ACGACGACCG	TGCCTCAAGA	CGCAGTGTCG	CGCTCGCAGC	GGCGGGGTAG
1401	GACTGGCAGG	GGTAGGAGAG	GCATCTACAG	GTTTGTGACT	CCGGGAGAAC
1451	GGCCCTCGGG	CATGTTCGAT	TCCTCGGTCC	TGTGTGAGTG	CTATGACGCG
1501	GGCTGTGCTT	GGTACGAGCT	CACCCCCGCC	GAGACCTCGG	TTAGGTTGCG
1551	GGCCTACCTG	AACACACCAG	GGTTGCCCGT	TTGCCAGGAC	CACCTGGAGT
1601	TCTGGGAGAG	TGTCTTCACA	GGCCTCACCC	ACATAGATGC	ACACTTCTTG
1651	TCCCAGACCA	AGCAGGCAGG	AGACAACTTC	CCCTACCTGG	TAGCATACCA

FIG. 2A

1701 AGCCACGGTG TGCGCCAGGG CTCAGGCCCC ACCTCCATCA TGGGATCAAA
1751 TGTGGAAGTG TCTCATACGG CTGAAACCTA CGCTGCACGG GCCAACACCC
1801 TTGCTGTACA GGCTGGGAGC CGTCCAAAAT GAGGTCACCC TCACCCACCC
1851 CATAACCAAA TACATCATGG CATGCATGTC GGCTGACCTG GAGGTCGTCA
1901 CTAGCACCTG GGTGCTGGTG GGCGGAGTCC TTGCAGCTCT GGCCGCGTAT
1951 TGCCTGACAA CAGGCAGTGT GGTCATTGTG GGTAGGATTA TCTTGTCCGG
2001 GAGGCCGGCT ATTGTTCCCG ACAGGGAGTT TCTCTACCAG GAGTTCGATG
2051 AAATGGAAGA GTGCGCCTCG CACCTCCCTT ACATCGAGCA GGGAATGCAG
2101 CTCGCCGAGC AATTCAAGCA GAAAGCGCTC GGGTTACTGC AAACAGCCAC
2151 CAAACAAGCG GAGGCTGCTG CTCCCGTGGT GGAGTCCAAG TGGCGAGCCC
2201 TTGAGACATT CTGGGCGAAG CACATGTGGA ATTTCATCAG CGGGATACAG
2251 TACTTAGCAG GCTTATCCAC TCTGCCTGGG AACCCCGCAA TAGCATCATT
2301 GATGGCATTC ACAGCCTCTA TCACCAGCCC GCTCACCACC CAAAGTACCC
2351 TCCTGTTTAA CATCTTGGGG GGGTGGGTGG CTGCCCAACT CGCCCCCCCC
2401 AGCGCCGCTT CGGCTTTCGT GGGCGCCGGC ATCGCCGGTG CGGCTGTTGG
2451 CAGCATAGGC CTTGGGAAGG TGCTTGTGGA CATTCTGGCG GGTTATGGAG
2501 CAGGAGTGGC CGGCGCGCTC GTGGCCTTCA AGGTCATGAG CGGCGAGATG
2551 CCCTCCACCG AGGACCTGGT CAATCTACTT CCTGCCATCC TCTCTCCTGG
2601 CGCCCTGGTC GTCGGGGTCG TGTGTGCAGC AATACTGCGT CGACACGTGG
2651 GTCCGGGAGA GGGGGCTGTG CAGTGGATGA ACCGGCTGAT AGCGTTCGCC
2701 TCGCGGGGTA ATCATGTTTC CCCCACGCAC TATGTGCCTG AGAGCGACGC
2751 CGCAGCGCGT GTTACTCAGA TCCTCTCCAG CCTTACCATC ACTCAGCTGC
2801 TGAAAAGGCT CCACCAGTGG ATTAATGAAG ACTGCTCCAC ACCGTGTTCC
2851 GGCTCGTGGC TAAGGGATGT TTGGGACTGG ATATGCACGG TGTTGACTGA
2901 CTTCAAGACC TGGCTCCAGT CCAAGCTCCT GCCGCAGCTA CCGGGAGTCC
2951 CTTTTTTCTC GTGCCAACGC GGGTACAAGG GAGTCTGGCG GGGAGACGGC
3001 ATCATGCAAA CCACCTGCCC ATGTGGAGCA CAGATCACCG GACATGTCAA
3051 AAACGGTTCC ATGAGGATCG TCGGGCCTAA GACCTGCAGC AACACGTGGC
3101 ATGGAACATT CCCCATCAAC GCATACACCA CGGGCCCCTG CACACCCTCT
3151 CCAGCGCCAA ACTATTCTAG GGCGCTGTGG CGGGTGGCCG CTGAGGAGTA
3201 CGTGGAGGTC ACGCGGGTGG GGGATTTCCA CTACGTGACG GGCATGACCA
3251 CTGACAACGT AAAGTGCCCA TGCCAGGTTC CGGCTCCTGA ATTCTTCACG
3301 GAGGTGGACG GAGTGCGGTT GCACAGGTAC GCTCCGGCGT GCAGGCCTCT
3351 CCTACGGGAG GAGGTTACAT TCCAGGTCGG GCTCAACCAA TACCTGGTTG

FIG. 2B

3401	GGTCACAGCT	ACCATGCGAG	CCCGAACCGG	ATGTAGCAGT	GCTCACTTCC
3451	ATGCTCACCG	ACCCCTCCCA	CATCACAGCA	GAAACGGCTA	AGCGTAGGTT
3501	GGCCAGGGGG	TCTCCCCCCT	CCTTGGCCAG	CTCTTCAGCT	AGCCAGTTGT
3551	CTGCGCCTTC	CTTGAAGGCG	ACATGCACTA	CCCACCATGT	CTCTCCGGAC
3601	GCTGACCTCA	TCGAGGCCAA	CCTCCTGTGG	CGGCAGGAGA	TGGGCGGGAA
3651	CATCACCCGC	GTGGAGTCGG	AGAACAAGGT	GGTAGTCCTG	GACTCTTTCG
3701	ACCCGCTTCG	AGCGGAGGAG	GATGAGAGGG	AAGTATCCGT	TCCGGCGGAG
3751	ATCCTGCGGA	AATCCAAGAA	GTTCCCCGCA	GCGATGCCCA	TCTGGGCGCG
3801	CCCGGATTAC	AACCCTCCAC	TGTTAGAGTC	CTGGAAGGAC	CCGGACTACG
3851	TCCCTCCGGT	GGTGCACGGG	TGCCCGTTGC	CACCTATCAA	GGCCCCTCCA
3901	ATACCACCTC	CACGGAGAAA	GAGGACGGTT	GTCCTAACAG	AGTCCTCCGT
3951	GTCTTCTGCC	TTAGCGGAGC	TCGCTACTAA	GACCTTCGGC	AGCTCCGAAT
4001	CATCGGCCGT	CGACAGCGGC	ACGGCGACCG	CCCTTCCTGA	CCAGGCCTCC
4051	GACGACGGTG	ACAAAGGATC	CGACGTTGAG	TCGTACTCCT	CCATGCCCCC
4101	CCTTGAGGGG	GAACCGGGGG	ACCCCGATCT	CAGTGACGGG	TCTTGGTCTA
4151	CCGTGAGCGA	GGAAGCTAGT	GAGGATGTCG	TCTGCTGCTC	AATGTCCTAC
4201	ACATGGACAG	GCGCCTTGAT	CACGCCATGC	GCTGCGGAGG	AAAGCAAGCT
4251	GCCCATCAAC	GCGTTGAGCA	ACTCTTTGCT	GCGCCACCAT	AACATGGTTT
4301	ATGCCACAAC	ATCTCGCAGC	GCAGGCCTGC	GGCAGAAGAA	GGTCACCTTT
4351	GACAGACTGC	AAGTCCTGGA	CGACCACTAC	CGGGACGTGC	TCAAGGAGAT
4401	GAAGGCGAAG	GCGTCCACAG	TTAAGGCTAA	ACTCCTATCC	GTAGAGGAAG
4451	CCTGCAAGCT	GACGCCCCCA	CATTCGGCCA	AATCCAAGTT	TGGCTATGGG
4501	GCAAAGGACG	TCCGGAACCT	ATCCAGCAAG	GCCGTTAACC	ACATCCACTC
4551	CGTGTGGAAG	GACTTGCTGG	AAGACACTGT	GACACCAATT	GACACCACCA
4601	TCATGGCAAA	AAATGAGGTT	TTCTGTGTCC	AACCAGAGAA	AGGAGGCCGT
4651	AAGCCAGCCC	GCCTTATCGT	ATTCCCAGAT	CTGGGAGTCC	GTGTATGCGA
4701	GAAGATGGCC	CTCTATGATG	TGGTCTCCAC	CCTTCCTCAG	GTCGTGATGG
4751	GCTCCTCATA	CGGATTCCAG	TACTCTCCTG	GGCAGCGAGT	CGAGTTCCTG
4801	GTGAATACCT	GGAAATCAAA	GAAAAACCCC	ATGGGCTTTT	CATATGACAC
4851	TCGCTGTTTC	GACTCAACGG	TCACCGAGAA	CGACATCCGT	GTTGAGGAGT
4901	CAATTTACCA	ATGTTGTGAC	TTGGCCCCCG	AAGCCAGACA	GGCCATAAAA
4951	TCGCTCACAG	AGCGGCTTTA	TATCGGGGGT	CCTCTGACTA	ATTCAAAAGG
5001	GCAGAACTGC	GGTTATCGCC	GGTGCCGCGC	GAGCGGCGTG	CTGACGACTA
5051	GCTGCGGTAA	CACCCTCACA	TGTTACTTGA	AGGCCTCTGC	AGCCTGTCGA

FIG. 2C

5101 GCTGCGAAGC TCCAGGACTG CACGATGCTC GTGAACGCCG CCGGCCTTGT
5151 CGTTATCTGT GAAAGCGCGG GAACCCAAGA GGACGCGGCG AGCCTACGAG
5201 TCTTCACGGA GGCTATGACT AGGTACTCTG CCCCCCCCGG GGACCCGCCC
5251 CAACCAGAAT ACGACTTGGA GCTGATAACA TCATGTTCCT CCAATGTGTC
5301 GGTCGCCCAC GATGCATCAG GCAAAAGGGT GTACTACCTC ACCCGTGATC
5351 CCACCACCCC CCTCGCACGG GCTGCGTGGG AAACAGCTAG ACACACTCCA
5401 GTTAACTCCT GGCTAGGCAA CATTATCATG TATGCGCCCA CTTTGTGGGC
5451 AAGGATGATT CTGATGACTC ACTTCTTCTC CATCCTTCTA GCACAGGAGC
5501 AACTTGAAAA AGCCCTGGAC TGCCAGATCT ACGGGGCCTG TTACTCCATT
5551 GAGCCACTTG ACCTACCTCA GATCATTGAA CGACTCCATG GCCTTAGCGC
5601 ATTTTCACTC CATAGTTACT CTCCAGGTGA GATCAATAGG GTGGCTTCAT
5651 GCCTCAGGAA ACTTGGGGTA CCACCCTTGC GAGTCTGGAG ACATCGGGCC
5701 AGGAGCGTCC GCGCTAGGCT ACTGTCCCAG GGGGGGAGGG CCGCCACTTG
5751 TGGCAAGTAC CTCTTCAACT GGGCAGTGAA GACCAAACTC AAACTCACTC
5801 CAATCCCGGC TGCGTCCCAG CTGGACTTGT CCGGCTGGTT CGTTGCTGGT
5851 TACAGCGGGG GAGACATATA TCACAGCCTG TCTCGTGCCC GACCCCGCTG
5901 GTTCATGCTG TGCCTACTCC TACTTTCTGT AGGGGTAGGC ATCTACCTGC
5951 TCCCCAACCG ATAAA

FIG. 2D

1 GCCACCATGG CCCCCATCAC CGCCTACAGC CAGCAGACCC GCGGCCTGCT
51 GGGCTGCATC ATCACCAGCC TGACCGGCCG CGACAAGAAC CAGGTGGAGG
101 GCGAGGTGCA GGTGGTGAGC ACCGCCACCC AGAGCTTCCT GGCCACCTGC
151 GTGAACGGCG TGTGCTGGAC CGTGTACCAC GGCGCCGGCA GCAAGACCCT
201 GGCCGGCCCC AAGGGCCCCA TCACCCAGAT GTACACCAAC GTGGACCAGG
251 ACCTGGTGGG CTGGCAGGCC CCCCCCGGCG CCCGCAGCCT GACCCCCTGC
301 ACCTGCGGCA GCAGCGACCT GTACCTGGTG ACCCGCCACG CCGACGTGAT
351 CCCCGTGCGC CGCCGCGGCG ACAGCCGCGG CAGCCTGCTG AGCCCCCGCC
401 CCGTGAGCTA CCTGAAGGGC AGCAGCGGCG GCCCCCTGCT GTGCCCCAGC
451 GGCCACGCCG TGGGCATCTT CCGCGCCGCC GTGTGCACCC GCGGCGTGGC
501 CAAGGCCGTG GACTTCGTGC CCGTGGAGAG CATGGAGACC ACCATGCGCA
551 GCCCCGTGTT CACCGACAAC AGCAGCCCCC CCGCCGTGCC CCAGAGCTTC
601 CAGGTGGCCC ACCTGCACGC CCCCACCGGC AGCGGCAAGA GCACCAAGGT
651 GCCCGCCGCC TACGCCGCCC AGGGCTACAA GGTGCTGGTG CTGAACCCCA
701 GCGTGGCCGC CACCCTGGGC TTCGGCGCCT ACATGAGCAA GGCCCACGGC
751 ATCGACCCCA ACATCCGCAC CGGCGTGCGC ACCATCACCA CCGGCGCCCC
801 CGTGACCTAC AGCACCTACG GCAAGTTCCT GGCCGACGGC GGCTGCAGCG
851 GCGGCGCCTA CGACATCATC ATCTGCGACG AGTGCCACAG CACCGACAGC
901 ACCACCATCC TGGGCATCGG CACCGTGCTG GACCAGGCCG AGACCGCCGG
951 CGCCCGCCTG GTGGTGCTGG CCACCGCCAC CCCCCCCGGC AGCGTGACCG
1001 TGCCCCACCC CAACATCGAG GAGGTGGCCC TGAGCAACAC CGGCGAGATC
1051 CCCTTCTACG GCAAGGCCAT CCCCATCGAG GCCATCCGCG GCGGCCGCCA
1101 CCTGATCTTC TGCCACAGCA AGAAGAAGTG CGACGAGCTG GCCGCCAAGC
1151 TGAGCGGCCT GGGCATCAAC GCCGTGGCCT ACTACCGCGG CCTGGACGTG
1201 AGCGTGATCC CCACCATCGG CGACGTGGTG GTGGTGGCCA CCGACGCCCT
1251 GATGACCGGC TACACCGGCG ACTTCGACAG CGTGATCGAC TGCAACACCT
1301 GCGTGACCCA GACCGTGGAC TTCAGCCTGG ACCCCACCTT CACCATCGAG
1351 ACCACCACCG TGCCCCAGGA CGCCGTGAGC CGCAGCCAGC GCCGCGGCCG
1401 CACCGGCCGC GGCCGCCGCG GCATCTACCG CTTCGTGACC CCCGGCGAGC
1451 GCCCCAGCGG CATGTTCGAC AGCAGCGTGC TGTGCGAGTG CTACGACGCC
1501 GGCTGCGCCT GGTACGAGCT GACCCCCGCC GAGACCAGCG TGCGCCTGCG
1551 CGCCTACCTG AACACCCCCG GCCTGCCCGT GTGCCAGGAC CACCTGGAGT
1601 TCTGGGAGAG CGTGTTCACC GGCCTGACCC ACATCGACGC CCACTTCCTG
1651 AGCCAGACCA AGCAGGCCGG CGACAACTTC CCCTACCTGG TGGCCTACCA

FIG. 3A

1701	GGCCACCGTG	TGCGCCCGCG	CCCAGGCCCC	CCCCCCCAGC	TGGGACCAGA
1751	TGTGGAAGTG	CCTGATCCGC	CTGAAGCCCA	CCCTGCACGG	CCCCACCCCC
1801	CTGCTGTACC	GCCTGGGCGC	CGTGCAGAAC	GAGGTGACCC	TGACCCACCC
1851	CATCACCAAG	TACATCATGG	CCTGCATGAG	CGCCGACCTG	GAGGTGGTGA
1901	CCAGCACCTG	GGTGCTGGTG	GGCGGCGTGC	TGGCCGCCCT	GGCCGCCTAC
1951	TGCCTGACCA	CCGGCAGCGT	GGTGATCGTG	GGCCGCATCA	TCCTGAGCGG
2001	CCGCCCCGCC	ATCGTGCCCG	ACCGCGAGTT	CCTGTACCAG	GAGTTCGACG
2051	AGATGGAGGA	GTGCGCCAGC	CACCTGCCCT	ACATCGAGCA	GGGCATGCAG
2101	CTGGCCGAGC	AGTTCAAGCA	GAAGGCCCTG	GGCCTGCTGC	AGACCGCCAC
2151	CAAGCAGGCC	GAGGCCGCCG	CCCCCGTGGT	GGAGAGCAAG	TGGCGCGCCC
2201	TGGAGACCTT	CTGGGCCAAG	CACATGTGGA	ACTTCATCAG	CGGCATCCAG
2251	TACCTGGCCG	GCCTGAGCAC	CCTGCCCGGC	AACCCCGCCA	TCGCCAGCCT
2301	GATGGCCTTC	ACCGCCAGCA	TCACCAGCCC	CCTGACCACC	CAGAGCACCC
2351	TGCTGTTCAA	CATCCTGGGC	GGCTGGGTGG	CCGCCCAGCT	GGCCCCCCCC
2401	AGCGCCGCCA	GCGCCTTCGT	GGGCGCCGGC	ATCGCCGGCG	CCGCCGTGGG
2451	CAGCATCGGC	CTGGGCAAGG	TGCTGGTGGA	CATCCTGGCC	GGCTACGGCG
2501	CCGGCGTGGC	CGGCGCCCTG	GTGGCCTTCA	AGGTGATGAG	CGGCGAGATG
2551	CCCAGCACCG	AGGACCTGGT	GAACCTGCTG	CCCGCCATCC	TGAGCCCCGG
2601	CGCCCTGGTG	GTGGGCGTGG	TGTGCGCCGC	CATCCTGCGC	CGCCACGTGG
2651	GCCCCGGCGA	GGGCGCCGTG	CAGTGGATGA	ACCGCCTGAT	CGCCTTCGCC
2701	AGCCGCGGCA	ACCACGTGAG	CCCCACCCAC	TACGTGCCCG	AGAGCGACGC
2751	CGCCGCCCGC	GTGACCCAGA	TCCTGAGCAG	CCTGACCATC	ACCCAGCTGC
2801	TGAAGCGCCT	GCACCAGTGG	ATCAACGAGG	ACTGCAGCAC	CCCCTGCAGC
2851	GGCAGCTGGC	TGCGCGACGT	GTGGGACTGG	ATCTGCACCG	TGCTGACCGA
2901	CTTCAAGACC	TGGCTGCAGA	GCAAGCTGCT	GCCCCAGCTG	CCCGGCGTGC
2951	CCTTCTTCAG	CTGCCAGCGC	GGCTACAAGG	GCGTGTGGCG	CGGCGACGGC
3001	ATCATGCAGA	CCACCTGCCC	CTGCGGCGCC	CAGATCACCG	GCCACGTGAA
3051	GAACGGCAGC	ATGCGCATCG	TGGGCCCCAA	GACCTGCAGC	AACACCTGGC
3101	ACGGCACCTT	CCCCATCAAC	GCCTACACCA	CCGGCCCCTG	CACCCCCAGC
3151	CCCGCCCCCA	ACTACAGCCG	CGCCCTGTGG	CGCGTGGCCG	CCGAGGAGTA
3201	CGTGGAGGTG	ACCCGCGTGG	GCGACTTCCA	CTACGTGACC	GGCATGACCA
3251	CCGACAACGT	GAAGTGCCCC	TGCCAGGTGC	CCGCCCCCGA	GTTCTTCACC
3301	GAGGTGGACG	GCGTGCGCCT	GCACCGCTAC	GCCCCCGCCT	GCCGCCCCCT
3351	GCTGCGCGAG	GAGGTGACCT	TCCAGGTGGG	CCTGAACCAG	TACCTGGTGG

FIG. 3B

3401	GCAGCCAGCT	GCCCTGCGAG	CCCGAGCCCG	ACGTGGCCGT	GCTGACCAGC
3451	ATGCTGACCG	ACCCCAGCCA	CATCACCGCC	GAGACCGCCA	AGCGCCGCCT
3501	GGCCCGCGGC	AGCCCCCCCA	GCCTGGCCAG	CAGCAGCGCC	AGCCAGCTGA
3551	GCGCCCCCAG	CCTGAAGGCC	ACCTGCACCA	CCCACCACGT	GAGCCCCGAC
3601	GCCGACCTGA	TCGAGGCCAA	CCTGCTGTGG	CGCCAGGAGA	TGGGCGGCAA
3651	CATCACCCGC	GTGGAGAGCG	AGAACAAGGT	GGTGGTGCTG	GACAGCTTCG
3701	ACCCCCTGCG	CGCCGAGGAG	GACGAGCGCG	AGGTGAGCGT	GCCCGCCGAG
3751	ATCCTGCGCA	AGAGCAAGAA	GTTCCCCGCC	GCCATGCCCA	TCTGGGCCCG
3801	CCCCGACTAC	AACCCCCCCC	TGCTGGAGAG	CTGGAAGGAC	CCCGACTACG
3851	TGCCCCCCGT	GGTGCACGGC	TGCCCCCTGC	CCCCCATCAA	GGCCCCCCCC
3901	ATCCCCCCCC	CCCGCCGCAA	GCGCACCGTG	GTGCTGACCG	AGAGCAGCGT
3951	GAGCAGCGCC	CTGGCCGAGC	TGGCCACCAA	GACCTTCGGC	AGCAGCGAGA
4001	GCAGCGCCGT	GGACAGCGGC	ACCGCCACCG	CCCTGCCCGA	CCAGGCCAGC
4051	GACGACGGCG	ACAAGGGCAG	CGACGTGGAG	AGCTACAGCA	GCATGCCCCC
4101	CCTGGAGGGC	GAGCCCGGCG	ACCCCGACCT	GAGCGACGGC	AGCTGGAGCA
4151	CCGTGAGCGA	GGAGGCCAGC	GAGGACGTGG	TGTGCTGCAG	CATGAGCTAC
4201	ACCTGGACCG	GCGCCCTGAT	CACCCCCTGC	GCCGCCGAGG	AGAGCAAGCT
4251	GCCCATCAAC	GCCCTGAGCA	ACAGCCTGCT	GCGCCACCAC	AACATGGTGT
4301	ACGCCACCAC	CAGCCGCAGC	GCCGGCCTGC	GCCAGAAGAA	GGTGACCTTC
4351	GACCGCCTGC	AGGTGCTGGA	CGACCACTAC	CGCGACGTGC	TGAAGGAGAT
4401	GAAGGCCAAG	GCCAGCACCG	TGAAGGCCAA	GCTGCTGAGC	GTGGAGGAGG
4451	CCTGCAAGCT	GACCCCCCCC	CACAGCGCCA	AGAGCAAGTT	CGGCTACGGC
4501	GCCAAGGACG	TGCGCAACCT	GAGCAGCAAG	GCCGTGAACC	ACATCCACAG
4551	CGTGTGGAAG	GACCTGCTGG	AGGACACCGT	GACCCCCATC	GACACCACCA
4601	TCATGGCCAA	GAACGAGGTG	TTCTGCGTGC	AGCCCGAGAA	GGGCGGCCGC
4651	AAGCCCGCCC	GCCTGATCGT	GTTCCCCGAC	CTGGGCGTGC	GCGTGTGCGA
4701	GAAGATGGCC	CTGTACGACG	TGGTGAGCAC	CCTGCCCCAG	GTGGTGATGG
4751	GCAGCAGCTA	CGGCTTCCAG	TACAGCCCCG	GCCAGCGCGT	GGAGTTCCTG
4801	GTGAACACCT	GGAAGAGCAA	GAAGAACCCC	ATGGGCTTCA	GCTACGACAC
4851	CCGCTGCTTC	GACAGCACCG	TGACCGAGAA	CGACATCCGC	GTGGAGGAGA
4901	GCATCTACCA	GTGCTGCGAC	CTGGCCCCCG	AGGCCCGCCA	GGCCATCAAG
4951	AGCCTGACCG	AGCGCCTGTA	CATCGGCGGC	CCCCTGACCA	ACAGCAAGGG
5001	CCAGAACTGC	GGCTACCGCC	GCTGCCGCGC	CAGCGGCGTG	CTGACCACCA
5051	GCTGCGGCAA	CACCCTGACC	TGCTACCTGA	AGGCCAGCGC	CGCCTGCCGC

FIG. 3C

5101 GCCGCCAAGC TGCAGGACTG CACCATGCTG GTGAACGCCG CCGGCCTGGT
5151 GGTGATCTGC GAGAGCGCCG GCACCCAGGA GGACGCCGCC AGCCTGCGCG
5201 TGTTCACCGA GGCCATGACC CGCTACAGCG CCCCCCCCGG CGACCCCCCC
5251 CAGCCCGAGT ACGACCTGGA GCTGATCACC AGCTGCAGCA GCAACGTGAG
5301 CGTGGCCCAC GACGCCAGCG GCAAGCGCGT GTACTACCTG ACCCGCGACC
5351 CCACCACCCC CCTGGCCCGC GCCGCCTGGG AGACCGCCCG CCACACCCCC
5401 GTGAACAGCT GGCTGGGCAA CATCATCATG TACGCCCCCA CCCTGTGGGC
5451 CCGCATGATC CTGATGACCC ACTTCTTCAG CATCCTGCTG GCCCAGGAGC
5501 AGCTGGAGAA GGCCCTGGAC TGCCAGATCT ACGGCGCCTG CTACAGCATC
5551 GAGCCCCTGG ACCTGCCCCA GATCATCGAG CGCCTGCACG GCCTGAGCGC
5601 CTTCAGCCTG CACAGCTACA GCCCCGGCGA GATCAACCGC GTGGCCAGCT
5651 GCCTGCGCAA GCTGGGCGTG CCCCCCCTGC GCGTGTGGCG CCACCGCGCC
5701 CGCAGCGTGC GCGCCCGCCT GCTGAGCCAG GGCGGCCGCG CCGCCACCTG
5751 CGGCAAGTAC CTGTTCAACT GGGCCGTGAA GACCAAGCTG AAGCTGACCC
5801 CCATCCCCGC CGCCAGCCAG CTGGACCTGA GCGGCTGGTT CGTGGCCGGC
5851 TACAGCGGCG GCGACATCTA CCACAGCCTG AGCCGCGCCC GCCCCCGCTG
5901 GTTCATGCTG TGCCTGCTGC TGCTGAGCGT GGGCGTGGGC ATCTACCTGC
5951 TGCCCAACCG CTAAA

FIG. 3D

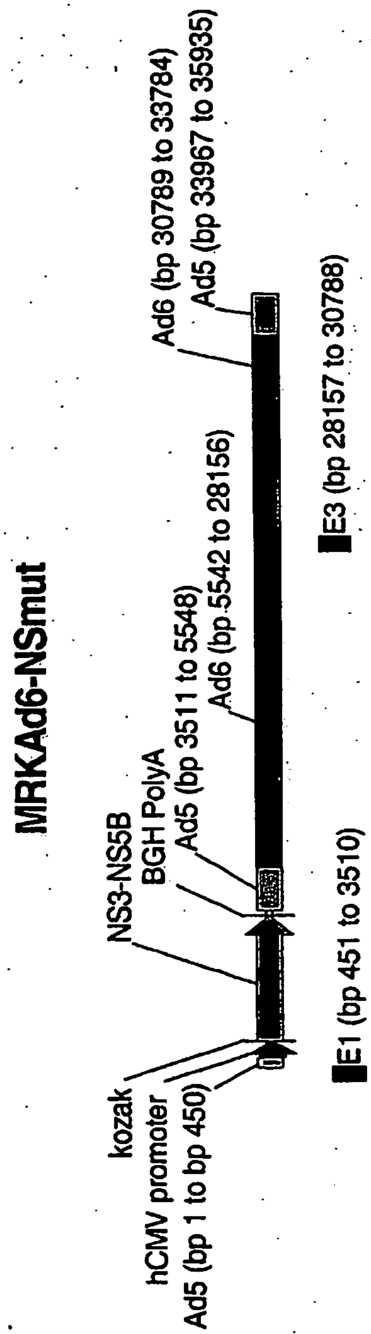
MRKAd6-NSmut
kozak
hCMV promoter
Ad5 (bp 1 to bp 450)
NS3-NS5B
BGH PolyA
Ad5 (bp 3511 to 5548)
Ad6 (bp 5542 to 28156)
Ad6 (bp 30789 to 33784)
Ad5 (bp 33967 to 35935)
E1 (bp 451 to 3510)
E3 (bp 28157 to 30788)

FIG. 4A

```
   1 catcatcaat aatatacctt attttggatt gaagccaata tgataatgag ggggtggagt
  61 ttgtgacgtg gcgcggggcg tgggaacggg gcgggtgacg tagtagtgtg gcggaagtgt
 121 gatgttgcaa gtgtggcgga acacatgtaa gcgacggatg tggcaaaagt gacgtttttg
 181 gtgtgcgccg gtgtacacag gaagtgacaa ttttcgcgcg gttttaggcg gatgttgtag
 241 taaatttggg cgtaaccgag taagatttgg ccattttcgc gggaaaactg aataagagga
 301 agtgaaatct gaataatttt gtgttactca tagcgcgtaa tatttgtcta gggccgcggg
 361 gactttgacc gtttacgtgg agactcgccc aggtgttttt ctcaggtgtt ttccgcgttc
 421 cgggtcaaag ttggcgtttt attattatag gcggccgcga tccattgcat acgttgtatc
 481 catatcataa tatgtacatt tatattggct catgtccaac attaccgcca tgttgacatt
 541 gattattgac tagttattaa tagtaatcaa ttacggggtc attagttcat agcccatata
 601 tggagttccg cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc
 661 cccgcccatt gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc
 721 attgacgtca atgggtggag tatttacggt aaactgccca cttggcagta catcaagtgt
 781 atcatatgcc aagtacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt
 841 atgcccagta catgacctta tgggactttc ctacttggca gtacatctac gtattagtca
 901 tcgctattac catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg
 961 actcacgggg atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc
1021 aaaatcaacg ggactttcca aaatgtcgta acaactccgc cccattgacg caaatgggcg
1081 gtaggcgtgt acggtgggag gtctatataa gcagagctcg tttagtgaac cgtcagatcg
1141 cctggagacg ccatccacgc tgttttgacc tccatagaag acaccgggac cgatccagcc
1201 tccgcggccg ggaacggtgc attggaacgc ggattccccg tgccaagagt gagatctgcc
1261 accatggcgc ccatcacggc ctactcccaa cagacgcggg gcctacttgg ttgcatcatc
1321 actagcctta caggccggga caagaaccag gtcgagggag aggttcaggt ggtttccacc
1381 gcaacacaat ccttcctggc gacctgcgtc aacggcgtgt gttggaccgt ttaccatggt
1441 gctggctcaa agacccttagc cggcccaaag ggccaatca cccagatgta cactaatgtg
1501 gaccaggacc tcgtcggctg gcaggcgccc cccgggcgc gttccttgac accatgcacc
1561 tgtggcagct cagaccttta cttggtcacg agacatgctg acgtcattcc ggtgcgccgg
1621 cggggcgaca gtagggggag cctgctctcc cccaggcctg tctcctactt gaagggctct
1681 tcgggtggtc cactgctctg cccttcgggg cacgctgtgg gcatcttccg ggctgccgta
1741 tgcacccggg gggttgcgaa ggcggtggac tttgtgcccg tagagtccat ggaaactact
1801 atgcggtctc cggtcttcac ggacaactca tcccccccgg ccgtaccgca gtcatttcaa
1861 gtggcccacc tacacgctcc cactggcagc ggcaagagta ctaaagtgcc ggctgcatat
1921 gcagcccaag ggtacaaggt gctcgtcctc aatccgtccg ttgccgctac cttagggttt
1981 ggggcgtata tgtctaaggc acacggtatt gaccccaaca tcagaactgg ggtaaggacc
2041 attaccacag gcgcccccgt cacatactct acctatggca agtttcttgc cgatggtggt
2101 tgctctgggg gcgcttatga catcataata tgtgatgagt gccattcaac tgactcgact
2161 acaatcttgg gcatcggcac agtcctggac caagcggaga cggctggagc gcggcttgtc
2221 gtgctcgcca ccgctacgcc tccgggatcg gtcaccgtgc cacacccaaa catcgaggag
2281 gtggccctgt ctaatactgg agagatcccc ttctatggca aagccatccc cattgaagcc
2341 atcagggggg gaaggcatct catttctgt cattccaaga agaagtgcga cgagctcgcc
2401 gcaaagctgt caggcctcgg aatcaacgct gtggcgtatt accgggggct cgatgtgtcc
2461 gtcataccaa ctatcggaga cgtcgttgtc gtggcaacag acgctctgat gacgggctat
2521 acgggcgact ttgactcagt gatcgactgt aacacatgtg tcacccagac agtcgacttc
2581 agcttggatc ccaccttcac cattgagacg acgaccgtgc ctcaagacgc agtgtcgcgc
2641 tcgcagcggc ggggtaggac tggcaggggt aggagaggca tctacaggtt tgtgactccg
2701 ggagaacggc cctcgggcat gttcgattcc tcggtcctgt gtgagtgcta tgacgcgggc
2761 tgtgcttggt acgagctcac ccccgccgag acctcggtta ggttgcgggc ctacctgaac
2821 acaccagggt tgcccgtttg ccaggaccac ctggagttct gggagagtgt cttcacaggc
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2941 tacctggtag cataccaagc cacggtgtgc gccagggctc aggccccacc tccatcatgg
3001 gatcaaatgt ggaagtgtct catacggctg aaacctacgc tgcacgggcc aacacccttg
3061 ctgtacaggc tgggagccgt ccaaaatgag gtcaccctca cccaccccat aaccaaatac
3121 atcatggcat gcatgtcggc tgacctggag gtcgtcacta gcacctgggt gctggtgggc
3181 ggagtccttg cagctctggc cgcgtattgc ctgacaacag gcagtgtggt cattgtgggt
3241 aggattatct tgtccgggag gccggctatt gttcccgaca gggagtttct ctaccaggag
```

FIG. 4B

3361 gccgagcaat tcaagcagaa agcgctcggg ttactgcaaa cagccaccaa acaagcggag
3421 gctgctgctc ccgtggtgga gtccaagtgg cgagcccttg agacattctg ggcgaagcac
3481 atgtggaatt tcatcagcgg gatacagtac ttagcaggct tatccactct gcctgggaac
3541 cccgcaatag catcattgat ggcattcaca gcctctatca ccagcccgct caccacccaa
3601 agtaccctcc tgtttaacat cttggggggg tgggtggctg cccaactcgc cccccccagc
3661 gccgcttcgg ctttcgtggg cgccggcatc gccggtgcgg ctgttggcag cataggcctt
3721 gggaaggtgc ttgtggacat tctggcgggt tatggagcag gagtggccgg cgcgctcgtg
3781 gccttcaagg tcatgagcgg cgagatgccc tccaccgagg acctggtcaa tctacttcct
3841 gccatcctct ctcctggcgc cctggtcgtc ggggtcgtgt gtgcagcaat actgcgtcga
3901 cacgtgggtc cgggagaggg ggctgtgcag tggatgaacc ggctgatagc gttcgcctcg
3961 cggggtaatc atgtttcccc cacgcactat gtgcctgaga gcgacgccgc agcgcgtgtt
4021 actcagatcc tctccagcct taccatcact cagctgctga aaaggctcca ccagtggatt
4081 aatgaagact gctccacacc gtgttccggc tcgtggctaa gggatgtttg ggactggata
4141 tgcacggtgt tgactgactt caagacctgg ctccagtcca agctcctgcc gcagctaccg
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4381 tacaccacgg gcccctgcac accctctcca gcgccaaact attctagggc gctgtggcgg
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5401 tggtctaccg tgagcgagga agctagtgag gatgtcgtct gctgctcaat gtcctacaca
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5581 ggcctgcggc agaagaaggt cacctttgac agactgcaag tcctggacga ccactaccgg
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5701 gaggaagcct gcaagctgac gcccccacat tcggccaaat ccaagtttgg ctatggggca
5761 aaggacgtcc ggaacctatc cagcaaggcc gttaaccaca tccactccgt gtggaaggac
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6061 aatacctgga aatcaaagaa aaaccccatg ggcttttcat atgacactcg ctgtttcgac
6121 tcaacggtca ccgagaacga catccgtgtt gaggagtcaa tttaccaatg ttgtgacttg
6181 gcccccgaag ccagacaggc cataaaatcg ctcacagagc ggctttatat cgggggtcct
6241 ctgactaatt caaaagggca gaactgcggt tatcgccggt gccgcgcgag cggcgtgctg
6301 acgactagct gcggtaacac cctcacatgt tacttgaagg cctctgcagc ctgtcgagct
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6481 tactctgccc cccccgggga cccgccccaa ccagaatacg acttggagct gataacatca
6541 tgttcctcca atgtgtcggt cgcccacgat gcatcaggca aaagggtgta ctacctcacc
6601 cgtgatccca ccacccccct cgcacgggct gcgtgggaaa cagctagaca cactccagtt

FIG. 4C

6661 aactcctggc taggcaacat tatcatgtat gcgcccactt tgtgggcaag gatgattctg
6721 atgactcact tcttctccat ccttctagca caggagcaac ttgaaaaagc cctggactgc
6781 cagatctacg gggcctgtta ctccattgag ccacttgacc tacctcagat cattgaacga
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7141 cgtgcccgac cccgctggtt catgctgtgc ctactcctac tttctgtagg ggtaggcatc
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7501 ggaaagaata tataaggtgg gggtcttatg tagttttgta tctgttttgc agcagccgcc
7561 gccgccatga gcaccaactc gtttgatgga agcattgtga gctcatattt gacaacgcgc
7621 atgcccccat gggccggggt gcgtcagaat gtgatgggct ccagcattga tggtcgcccc
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7741 actgcagcct ccgccgccgc ttcagccgct gcagccaccg cccgcgggat tgtgactgac
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7981 gcggtttaaa acataaataa aaaaccagac tctgtttgga tttggatcaa gcaagtgtct
8041 tgctgtcttt atttaggggt tttgcgcgcg cggtaggccc gggaccagcg gtctcggtcg
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8221 gtggtgttgt agatgatcca gtcgtagcag gagcgctggg cgtggtgcct aaaaatgtct
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8341 agctgggatg ggtgcatacg tggggatatg agatgcatct tggactgtat ttttaggttg
8401 gctatgttcc cagccatatc cctccgggga ttcatgttgt gcagaaccac cagcacagtg
8461 tatccggtgc acttgggaaa tttgtcatgt agcttagaag gaaatgcgtg gaagaacttg
8521 gagacgccct tgtgacctcc aagattttcc atgcattcgt ccataatgat ggcaatgggc
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9181 cctcgtttcg cgggttgggg cggctttcgc tgtacggcag tagtcggtgc tcgtccagac
9241 gggccagggt catgtctttc cacgggcgca gggtcctcgt cagcgtagtc tgggtcacgg
9301 tgaaggggtg cgctccgggc tgcgcgctgg ccagggtgcg cttgaggctg gtcctgctgg
9361 tgctgaagcg ctgccggtct tcgccctgcg cgtcggccag gtagcatttg accatggtgt
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9601 tgagctctgg ccgttcgggg tcaaaaacca ggtttccccc atgctttttg atgcgtttct
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9781 actcggacca ctctgagacg aaggctcgcg tccaggccag cacgaaggag gctaagtggg
9841 aggggtagcg gtcgttgtcc actagggggt ccactcgctc cagggtgtga agacacatgt
9901 cgccctcttc ggcatcaagg aaggtgattg gtttataggt gtaggccacg tgaccgggtg

FIG. 4D

```
 9961 ttcctgaagg ggggctataa aagggggtgg gggcgcgttc gtcctcactc tcttccgcat
10021 cgctgtctgc gagggccagc tgttggggtg agtactccct ctcaaaagcg ggcatgactt
10081 ctgcgctaag attgtcagtt tccaaaaacg aggaggattt gatattcacc tggcccgcgg
10141 tgatgccttt gagggtggcc gcgtccatct ggtcagaaaa gacaatcttt ttgttgtcaa
10201 gcttggtggc aaacgacccg tagagggcgt tggacagcaa cttggcgatg gagcgcaggg
10261 tttggttttt gtcgcgatcg gcgcgctcct tggccgcgat gtttagctgc acgtattcgc
10321 gcgcaacgca ccgccattcg ggaaagacgg tggtgcgctc gtcgggcact aggtgcacgc
10381 gccaaccgcg gttgtgcagg gtgacaaggt caacgctggt ggctacctct ccgcgtaggc
10441 gctcgttggt ccagcagagg cggccgccct tgcgcgagca gaatggcggt agtgggtcta
10501 gctgcgtctc gtccgggggg tctgcgtcca cggtaaagac cccgggcagc aggcgcgcgt
10561 cgaagtagtc tatcttgcat ccttgcaagt ctagcgcctg ctgccatgcg cgggcggcaa
10621 gcgcgcgctc gtatgggttg agtgggggac cccatggcat ggggtgggtg agcgcggagg
10681 cgtacatgcc gcaaatgtcg taaacgtaga ggggctctct gagtattcca agatatgtag
10741 ggtagcatct tccaccgcgg atgctggcgc gcacgtaatc gtatagttcg tgcgagggag
10801 cgaggaggtc gggaccgagg ttgctacggg cgggctgctc tgctcggaag actatctgcc
10861 tgaagatggc atgtgagttg gatgatatgg ttggacgctg gaagacgttg aagctggcgt
10921 ctgtgagacc taccgcgtca cgcacgaagg aggcgtagga gtcgcgcagc ttgttgacca
10981 gctcggcggt gacctgcacg tctagggcgc agtagtccag ggtttccttg atgatgtcat
11041 acttatcctg tccctttttt ttccacagct cgcggttgag gacaaactct tcgcggtctt
11101 tccagtactc ttggatcgga aacccgtcgg cctccgaacg gtaagagcct agcatgtaga
11161 actggttgac ggcctggtag gcgcagcatc cctttctac gggtagcgcg tatgcctgcg
11221 cggccttccg gagcgaggtg tgggtgagcg caaaggtgtc cctaaccatg actttgaggt
11281 actggtattt gaagtcagtg tcgtcgcatc cgccctgctc ccagagcaaa aagtccgtgc
11341 gctttttgga acgcgggttt ggcagggcga aggtgacatc gttgaagagt atctttcccg
11401 cgcgaggcat aaagttgcgt gtgatgcgga agggtcccgg cacctcggaa cggttgttaa
11461 ttacctgggc ggcgagcacg atctcgtcaa agccgttgat gttgtggccc acaatgtaaa
11521 gttccaagaa gcgcgggatg cccttgatgg aaggcaattt tttaagttcc tcgtaggtga
11581 gctcttcagg ggagctgagc ccgtgctctg aaagggccca gtctgcaaga tgagggttgg
11641 aagcgacgaa tgagctccac aggtcacggg ccattagcat ttgcaggtgg tcgcgaaagg
11701 tcctaaactg gcgacctatg gccatttttt ctggggtgat gcagtagaag gtaagcgggt
11761 cttgttccca gcggtcccat ccaaggtccg cggctaggtc tcgcgcggcg gtcactagag
11821 gctcatctcc gccgaacttc atgaccagca tgaagggcac gagctgcttc ccaaaggccc
11881 ccatccaagt ataggtctct acatcgtagg tgacaaagag acgctcggtg cgaggatgcg
11941 agccgatcgg gaagaactgg atctcccgcc accagttgga ggagtggctg ttgatgtggt
12001 gaaagtagaa gtccctgcga cgggccgaac actcgtgctg gcttttgtaa aaacgtgcgc
12061 agtactggca gcggtgcacg ggctgtacat cctgcacgag gttgacctga cgaccgcgca
12121 caaggaagca gagtgggaat ttgagcccct cgcctggcgg gtttggctgg tggtcttcta
12181 cttcggctgc ttgtccttga ccgtctggct gctcgagggg agttacggtg gatcggacca
12241 ccacgccgcg cgagcccaaa gtccagatgt ccgcgcgcgg cggtcggagc ttgatgacaa
12301 catcgcgcag atgggagctg tccatggtct ggagctcccg cggcgtcagg tcaggcggga
12361 gctcctgcag gtttacctcg catagccggg tcagggcgcg ggctaggtcc aggtgatacc
12421 tgatttccag gggctggttg gtggcggcgt cgatggcttg caagaggccg catccccgcg
12481 gcgcgactac ggtaccgcgc ggcgggcggt gggccgcggg ggtgtccttg gatgatgcat
12541 ctaaaagcgg tgacgcgggc gggcccccgg aggtaggggg ggctcgggac ccgccgggag
12601 agggggcagg ggcacgtcgg cgccgcgcgc gggcaggagc tggtgctgcg cgcggaggtt
12661 gctggcgaac gcgacgacgc ggcggttgat ctcctgaatc tggcgcctct gcgtgaagac
12721 gacgggcccg gtgagcttga acctgaaaga gagttcgaca gaatcaattt cggtgtcgtt
12781 gacggcggcc tggcgcaaaa tctcctgcac gtctcctgag ttgtcttgat aggcgatctc
12841 ggccatgaac tgctcgatct cttcctcctg gagatctccg cgtccggctc gctccacggt
12901 ggcggcgagg tcgttggaga tgcgggccat gagctgcgag aaggcgttga ggcctccctc
12961 gttccagacg cggctgtaga ccacgccccc ttcggcatcg cgggcgcgca tgaccacctg
13021 cgcgagattg agctccacgt gccgggcgaa gacggcgtag tttcgcaggc gctgaaagag
13081 gtagttgagg gtggtggcgg tgtgttctgc cacgaagaag tacataaccc agcgccgcaa
13141 cgtggattcg ttgatatccc ccaaggcctc aaggcgctcc atggcctcgt agaagtccac
13201 ggcgaagttg aaaaactggg agttgcgcgc cgacacggtt aactcctcct ccagaagacg
```

FIG. 4E

13261 gatgagctcg gcgacagtgt cgcgcacctc gcgctcaaag gctacagggg cctcttcttc
13321 ttcttcaatc tcctcttcca taagggcctc cccttcttct tcttctggcg gcggtggggg
13381 aggggggaca cggcggcgac gacggcgcac cgggaggcgg tcgacaaagc gctcgatcat
13441 ctccccgcgg cgacggcgca tggtctcggt gacggcgcgg ccgttctcgc gggggcgcag
13501 ttggaagacg ccgcccgtca tgtcccggtt atgggttggc ggggggctgc cgtgcggcag
13561 ggatacggcg ctaacgatgc atctcaacaa ttgttgtgta ggtactccgc caccgaggga
13621 cctgagcgag tccgcatcga ccggatcgga aaacctctcg agaaaggcgt ctaaccagtc
13681 acagtcgcaa ggtaggctga gcaccgtggc gggcggcagc gggcggcggt cggggttgtt
13741 tctggcggag gtgctgctga tgatgtaatt aaagtaggcg gtcttgagac ggcggatggt
13801 cgacagaagc accatgtcct tgggtccggc ctgctgaatg cgcaggcggt cggccatgcc
13861 ccaggcttcg ttttgacatc ggcgcaggtc tttgtagtag tcttgcatga gcctttctac
13921 cggcacttct tcttctcctt cctcttgtcc tgcatctctt gcatctatcg ctgcggcggc
13981 ggcggagttt ggccgtaggt ggcgccctct tcctcccatg cgtgtgaccc cgaagcccct
14041 catcggctga agcagggcca ggtcggcgac aacgcgctcg gctaatatgg cctgctgcac
14101 ctgcgtgagg gtagactgga agtcgtccat gtccacaaag cggtggtatg cgcccgtgtt
14161 gatggtgtaa gtgcagttgg ccataacgga ccagttaacg gtctggtgac ccggctgcga
14221 gagctcggtg tacctgagac gcgagtaagc ccttgagtca aagacgtagt cgttgcaagt
14281 ccgcaccagg tactggtatc ccaccaaaaa gtgcggcggc ggctggcggt agaggggcca
14341 gcgtagggtg gccggggctc cgggggcgag gtcttccaac ataaggcgat gatatccgta
14401 gatgtacctg gacatccagg tgatgccggc ggcggtggtg gaggcgcgcg gaaagtcacg
14461 gacgcggttc cagatgttgc gcagcggcaa aaagtgctcc atggtcggga cgctctggcc
14521 ggtcaggcgc gcgcagtcgt tgacgctcta gaccgtgcaa aaggagagcc tgtaagcggg
14581 cactcttccg tggtctggtg gataaattcg caagggtatc atggcggacg accggggttc
14641 gaaccccgga tccggccgtc cgccgtgatc catgcggtta ccgcccgcgt gtcgaaccca
14701 ggtgtgcgac gtcagacaac gggggagcgc tccttttggc ttccttccag gcgcggcgga
14761 tgctgcgcta gctttttgg ccactggccg cgcgcggcgt aagcggttag gctggaaagc
14821 gaaagcatta agtggctcgc tccctgtagc cggagggtta ttttccaagg gttgagtcgc
14881 gggacccccg gttcgagtct cgggccggcc ggactgcggc gaacgggggt ttgcctcccc
14941 gtcatgcaag accccgcttg caaattcctc cggaaacagg gacgagcccc tttttgctt
15001 ttcccagatg catccggtgc tgcggcagat gcgcccccct cctcagcagc ggcaagagca
15061 agagcagcgg cagacatgca gggcaccctc cccttctcct accgcgtcag gaggggcaac
15121 atccgcggct gacgcggcgg cagatggtga ttacgaaccc ccgcggcgcc ggacccggca
15181 ctacttggac ttggaggagg gcgagggcct ggcgcggcta ggagcgccct ctcctgagcg
15241 acacccaagg gtgcagctga agcgtgacac gcgcgaggcg tacgtgccgc ggcagaacct
15301 gtttcgcgac cgcgagggag aggagcccga ggagatgcgg gatcgaaagt tccatgcagg
15361 gcgcgagttg cggcatggcc tgaaccgcga gcggttgctg cgcgaggagg actttgagcc
15421 cgacgcgcgg accgggatta gtcccgcgcg cgcacacgtg gcggccgccg acctggtaac
15481 cgcgtacgag cagacggtga accaggagat taactttcaa aaaagcttta acaaccacgt
15541 gcgcacgctt gtggcgcgcg aggaggtggc tataggactg atgcatctgt gggactttgt
15601 aagcgcgctg gagcaaaacc caaatagcaa gccgctcatg gcgcagctgt tccttatagt
15661 gcagcacagc agggacaacg aggcattcag ggatgcgctg ctaaacatag tagagcccga
15721 gggccgctgg ctgctcgatt tgataaacat tctgcagagc atagtggtgc aggagcgcag
15781 cttgagcctg gctgacaagg tggccgccat taactattcc atgctcagtc tgggcaagtt
15841 ttacgcccgc aagatatacc ataccccta cgttcccata gacaaggagg taaagatcga
15901 ggggttctac atgcgcatgg cgctgaaggt gcttaccttg agcgacgacc tgggcgttta
15961 tcgcaacgag cgcatccaca aggccgtgag cgtgagccgg cggcgcgagc tcagcgaccg
16021 cgagctgatg cacagcctgc aaagggccct ggctggcacg ggcagcggcg atagagaggc
16081 cgagtcctac tttgacgcgg gcgctgacct gcgctgggcc ccaagccgac gcgccctgga
16141 ggcagctggg gccggacctg ggctggcggt ggcacccgcg cgcgctggca acgtcggcgg
16201 cgtggaggaa tatgacgagg acgatgagta cgagccagag gacggcgagt actaagcggt
16261 gatgtttctg atcagatgat gcaagacgca acggacccgg cggtgcgggc ggcgctgcag
16321 agccagccgt ccggccttaa ctccacggac gactggcgcc aggtcatgga ccgcatcatg
16381 tcgctgactg cgcgcaaccc tgacgcgttc cggcagcagc cgcaggccaa ccggctctcc
16441 gcaattctgg aagcggtggt cccggcgcgc gcaaacccca cgcacgagaa ggtgctggcg
16501 atcgtaaacg cgctggccga aaacagggcc atccggcccg atgaggccgg cctggtctac

FIG. 4F

16561 gacgcgctgc ttcagcgcgt ggctcgttac aacagcagca acgtgcagac caacctggac
16621 cggctggtgg gggatgtgcg cgaggccgtg gcgcagcgtg agcgcgcgca gcagcagggc
16681 aacctgggct ccatggttgc actaaacgcc ttcctgagta cacagcccgc caacgtgccg
16741 cggggacagg aggactacac caactttgtg agcgcactgc ggctaatggt gactgagaca
16801 ccgcaaagtg aggtgtatca gtccgggcca gactattttt tccagaccag tagacaaggc
16861 ctgcagaccg taaacctgag ccaggctttc aagaacttgc aggggctgtg gggggtgcgg
16921 gctcccacag gcgaccgcgc gaccgtgtct agcttgctga cgcccaactc gcgcctgttg
16981 ctgctgctaa tagcgccctt cacggacagt ggcagcgtgt cccgggacac atacctaggt
17041 cacttgctga cactgtaccg cgaggccata ggtcaggcgc atgtggacga gcatactttc
17101 caggagatta caagtgttag ccgcgcgctg gggcaggagg acacgggcag cctggaggca
17161 accctgaact acctgctgac caaccggcgg caaaaaatcc cctcgttgca cagtttaaac
17221 agcgaggagg agcgcatttt gcgctatgtg cagcagagcg tgagccttaa cctgatgcgc
17281 gacggggtaa cgcccagcgt ggcgctggac atgaccgcgc gcaacatgga accgggcatg
17341 tatgcctcaa accggccgtt tatcaatcgc ctaatggact acttgcatcg cgcggccgcc
17401 gtgaaccccg agtatttcac caatgccatc ttgaacccgc actggctacc gccccctggt
17461 ttctacaccg ggggattcga ggtgcccgag ggtaacgatg gattcctctg ggacgacata
17521 gacgacagcg tgttttcccc gcaaccgcag accctgctag agttgcaaca acgcgagcag
17581 gcagaggcgg cgctgcgaaa ggaaagcttc cgcaggccaa gcagcttgtc cgatctaggc
17641 gctgcggccc cgcggtcaga tgctagtagc ccatttccaa gcttgatagg gtctcttacc
17701 agcactcgca ccacccgccc gcgcctgctg ggcgaggagg agtacctaaa caactcgctg
17761 ctgcagccgc agcgcgaaaa gaacctgcct ccggcgtttc ccaacaacgg gatagagagc
17821 ctagtggaca agatgagtag atggaagacg tatgcgcagg agcacaggga tgtgcccggc
17881 ccgcgcccgc ccacccgtcg tcaaaggcac gaccgtcagc ggggtctggt gtgggaggac
17941 gatgactcgg cagacgacag cagcgtcttg gatttgggag ggagtggcaa cccgtttgca
18001 caccttcgcc ccaggctggg gagaatgttt taaaaaaaag catgatgcaa aataaaaaac
18061 tcaccaaggc catggcaccg agcgttggtt ttcttgtatt ccccttagta tgcggcgcgc
18121 ggcgatgtat gaggaaggtc ctcctccctc ctacgagagc gtggtgagcg cggcgccagt
18181 ggcggcggcg ctgggttcac ccttcgatgc tcccctggac ccgccgttcg tgcctccgcg
18241 gtacctgcgg cctaccgggg ggagaaacag catccgttac tctgagttgg cacccctatt
18301 cgacaccacc cgtgtgtacc ttgtggacaa caagtcaacg gatgtggcat ccctgaacta
18361 ccagaacgac cacagcaact ttctaaccac ggtcattcaa aacaatgact acagcccggg
18421 ggaggcaagc acacagacca tcaatcttga cgaccggtcg cactggggcg gcgacctgaa
18481 aaccatcctg cataccaaca tgccaaatgt gaacgagttc atgtttacca ataagtttaa
18541 ggcgcgggtg atggtgtcgc gctcgcttac taaggacaaa caggtggagc tgaaatacga
18601 gtgggtggag ttcacgctgc ccgagggcaa ctactccgag accatgacca tagaccttat
18661 gaacaacgcg atcgtggagc actacttgaa agtgggcagg cagaacgggg ttctggaaag
18721 cgacatcggg gtaaagtttg acacccgcaa cttcagactg gggtttgacc cagtcactgg
18781 tcttgtcatg cctggggtat atacaaacga agccttccat ccagacatca ttttgctgcc
18841 aggatgcggg gtggacttca cccacagccg cctgagcaac ttgttgggca tccgcaagcg
18901 gcaacccttc caggagggct ttaggatcac ctacgatgac ctggagggtg gtaacattcc
18961 cgcactgttg gatgtggacg cctaccaggc aagcttgaaa gatgacaccg aacagggcgg
19021 gggtggcgca ggcggcggca acaacagtgg cagcggcgcg gaagagaact ccaacgcggc
19081 agctgcggca atgcagccgg tggaggacat gaacgatcat gccattcgcg gcgacacctt
19141 tgccacacgg gcggaggaga agcgcgctga ggccgaggca gcggccgaag ctgccgcccc
19201 cgctgcggag gctgcacaac ccgaggtcga gaagcctcag aagaaaccgg tgattaaacc
19261 cctgacagag gacagcaaga aacgcagtta caacctaata agcaatgaca gcaccttcac
19321 ccagtaccgc agctggtacc ttgcatacaa ctacggcgac cctcaggccg ggatccgctc
19381 atggaccctg ctttgcactc ctgacgtaac ctgcggctcg gagcaggtat actggtcgtt
19441 gcccgacatg atgcaagacc ccgtgacctt ccgctccacg cgccagatca gcaactttcc
19501 ggtggtgggc gccgagctgt tgcccgtgca ctccaagagc ttctacaacg accaggccgt
19561 ctactcccag ctcatccgcc agtttacctc tctgacccac gtgttcaatc gctttcccga
19621 gaaccagatt ttggcgcgcc cgccagcccc caccatcacc accgtcagtg aaaacgttcc
19681 tgctctcaca gatcacggga cgctaccgct gcgcaacagc atcggaggag tccagcgagt
19741 gaccattact gacgccagac gccgcacctg cccctacgtt tacaaggccc tgggcatagt
19801 ctcgccgcgc gtcctatcga gccgcacttt ttgagcaagc atgtccatcc ttatatcgcc

FIG. 4G

19861 cagcaataac acaggctggg gcctgcgctt cccaagcaag atgtttggcg gggccaagaa
19921 gcgctccgac caacacccag tgcgcgtgcg cgggcactac cgcgcgccct ggggcgcgca
19981 caaacgcggc cgcactgggc gcaccaccgt cgatgacgcc atcgacgcgg tggtggagga
20041 ggcgcgcaac tacacgccca cgccgccgcc agtgtccacc gtggacgcgg ccattcagac
20101 cgtggtgcgc ggagcccggc gctacgctaa aatgaagaga cggcggaggc gcgtagcacg
20161 tcgccaccgc cgccgacccg gcactgccgc ccaacgcgcg gcggcggccc tgcttaaccg
20221 cgcacgtcgc accggccgac gggcggccat gcgagccgct cgaaggctgg ccgcgggtat
20281 tgtcactgtg ccccccaggt ccaggcgacg agcggccgcc gcagcagccg cggccattag
20341 tgctatgact cagggtcgca ggggcaacgt gtactgggtg cgcgactcgg ttagcggcct
20401 gcgcgtgccc gtgcgcaccc gcccccgcg caactagatt gcaataaaaa actacttaga
20461 ctcgtactgt tgtatgtatc cagcggcggc ggcgcgcatc gaagctatgt ccaagcgcaa
20521 aatcaaagaa gagatgctcc aggtcatcgc gccggagatc tatggccccc cgaagaagga
20581 agagcaggat tacaagcccc gaaagctaaa gcgggtcaaa aagaaaaaga aagatgatga
20641 tgatgatgaa cttgacgacg aggtggaact gttgcacgcg accgcgccca ggcgacgggt
20701 acagtggaaa ggtcgacgcg taagacgtgt tttgcgaccc ggcaccaccg tagtctttac
20761 gcccggtgag cgctccaccc gcacctacaa gcgcgtgtat gatgaggtgt acggcgacga
20821 ggacctgctt gagcaggcca acgagcgcct cggggagttt gcctacggaa agcggcataa
20881 ggacatgctg gcgttgccgc tggacgaggg caacccaaca cctagcctaa agcccgtgac
20941 actgcagcag gtgctgcccg cgcttgcacc gtccgaagaa aagcgcggcc taaagcgcga
21001 gtctggtgac ttggcaccca ccgtgcagct gatggtaccc aagcgtcagc gactggaaga
21061 tgtcttggaa aaaatgaccg tggagcctgg gctggagccc gaggtccgcg tgcggccaat
21121 caagcaggtg gcaccgggac tgggcgtgca gaccgtggac gttcagatac ccaccaccag
21181 tagcactagt attgccactg ccacagaggg catggagaca caaacgtccc cggttgcctc
21241 ggcggtggca gatgccgcgg tgcaggcggc cgctgcggcc gcgtccaaga cctctacgga
21301 ggtgcaaacg gacccgtgga tgtttcgtgt ttcagccccc cggcgtccgc gccgttcaag
21361 gaagtacggc gccgccagcg cgctactgcc cgaatatgcc ctacatcctt ccatcgcgcc
21421 tacccccggc tatcgtggct acacctaccg ccccagaaga cgagcaacta cccgacgccg
21481 aaccaccact ggaacccgcc gccgccgtcg ccgtcgccag cccgtgctgg ccccgatttc
21541 cgtgcgcagg gtggctcgcg aaggaggcag gaccctggtg ctgccaacag cgcgctacca
21601 ccccagcatc gtttaaaagc cggtctttgt ggttcttgca gatatggccc tcacctgccg
21661 cctccgtttc ccggtgccgg gattccgagg aagaatgcac cgtaggaggg gcatggccgg
21721 ccacggcctg acgggcggca tgcgtcgtgc gcaccaccgg cggcggcgcg cgtcgcaccg
21781 tcgcatgcgc ggcggtatcc tgcccctcct tattccactg atcgccgcgg cgattggcgc
21841 cgtgcccgga attgcatccg tggccttgca ggcgcagaga cactgattaa aaacaagtta
21901 catgtggaaa aatcaaaata aaagtctgga ctctcacgct cgcttggtcc tgtaactatt
21961 ttgtagaatg gaagacatca actttgcgtc actggccccg cgacacggct cgcgcccgtt
22021 catgggaaac tggcaagata tcggcaccag caatatgagc ggtggcgcct tcagctgggg
22081 ctcgctgtgg agcggcatta aaaatttcgg ttccgccgtt aagaactatg gcagcaaagc
22141 ctggaacagc agcacaggcc agatgctgag ggacaagttg aaagagcaaa atttccaaca
22201 aaaggtggta gatggcctgg cctctggcat tagcggggtg gtggacctgg ccaaccaggc
22261 agtgcaaaat aagattaaca gtaagcttga tccccgccct cccgtagagg agcctccacc
22321 ggccgtggag acagtgtctc cagaggggcg tggcgaaaag cgtccgcgac ccgacaggga
22381 agaaactctg gtgacgcaaa tagacgagcc tccctcgtac gaggaggcac taaagcaagg
22441 cctgcccacc acccgtccca tcgcgcccat ggctaccgga gtgctgggcc agcacacacc
22501 cgtaacgctg gacctgcctc cccccgccga cacccagcag aaacctgtgc tgccaggccc
22561 gtccgccgtt gttgtaaccc gtcctagccg cgcgtccctg cgccgcgccg ccagcggtcc
22621 gcgatcgttg cggcccgtag ccagtggcaa ctggcaaagc acactgaaca gcatcgtggg
22681 tttgggggtg caatccctga agcgccgacg atgcttctga tagctaacgt gtcgtatgtg
22741 tgtcatgtat gcgtccatgt cgccgccaga ggagctgctg agccgccgcg cgcccgcttt
22801 ccaagatggc taccccttcg atgatgccgc agtggtctta catgcacatc tcgggccagg
22861 acgcctcgga gtacctgagc cccgggctgg tgcagttcgc ccgcgccacc gagacgtact
22921 tcagcctgaa taacaagttt agaaacccca cggtggcgcc tacgcacgac gtgaccacag
22981 accggtctca gcgtttgacg ctgcggttca tccccgtgga ccgcgaggat actgcgtact
23041 cgtacaaggc gcggttcacc ctagctgtgg gtgataaccg tgtgctagac atggcttcca
23101 cgtactttga catccgcggc gtgctggaca ggggccctac ttttaagccc tactctggca

FIG. 4H

23161 ctgcctacaa cgcactggcc cccaagggtg cccccaactc gtgcgagtgg gaacaaaatg
23221 aaactgcaca agtggatgct caagaacttg acgaagagga gaatgaagcc aatgaagctc
23281 aggcgcgaga acaggaacaa gctaagaaaa cccatgtata tgcccaggct ccactgtccg
23341 gaataaaaat aactaaagaa ggtctacaaa taggaactgc cgacgccaca gtagcaggtg
23401 ccggcaaaga aattttcgca gacaaaactt ttcaacctga accacaagta ggagaatctc
23461 aatggaacga agcggatgcc acagcagctg gtggaagggt tcttaaaaag acaactccca
23521 tgaaaccctg ctatggctca tacgctagac ccaccaattc caacggcgga cagggcgtta
23581 tggttgaaca aaatggtaaa ttggaaagtc aagtcgaaat gcaatttttt tccacatcca
23641 caaatgccac aaatgaagtt aacaatatac aaccaacagt tgtattgtac agcgaagatg
23701 taaacatgga aactccagat actcatcttt cttataaacc taaaatgggg gataaaaatg
23761 ccaaagtcat gcttggacaa caagcaatgc caaacagacc aaattacatt gcttttagag
23821 acaattttat tggtctcatg tattacaaca gcacaggtaa catgggtgtc cttgctggtc
23881 aggcatcgca gttgaacgct gttgtagatt tgcaagacag aaacacagag ctgtcctacc
23941 agcttttgct tgattcaatt ggcgacagaa caagatactt ttcaatgtgg aatcaagctg
24001 ttgacagcta tgatccagat gtcagaatta ttgagaacca tggaactgag gatgagttgc
24061 caaattattg ctttcctctt ggtggaattg ggattactga cacttttcaa gctgttaaaa
24121 caactgctgc taacggggac caaggcaata ctacctggca aaaagattca acatttgcag
24181 aacgcaatga aataggggtg ggaaataact ttgccatgga aattaacctg aatgccaacc
24241 tatggagaaa tttcctttac tccaatattg cgctgtacct gccagacaag ctaaaataca
24301 accccaccaa tgtggaaata tctgacaacc ccaacaccta cgactacatg aacaagcgag
24361 tggtggctcc tgggcttgta gactgctaca ttaaccttgg ggcgcgctgg tctctggact
24421 acatggacaa cgttaatccc tttaaccacc accgcaatgc gggcctgcgt taccgctcca
24481 tgttgttggg aaacggccgc tacgtgccct ttcacattca ggtgccccaa aagtttttg
24541 ccattaaaaa cctcctcctc ctgccaggct catacacata tgaatggaac ttcaggaagg
24601 atgttaacat ggttctgcag agctctctgg gaaacgacct tagagttgac ggggctagca
24661 ttaagtttga cagcatttgt ctttacgcca ccttcttccc catggcccac aacacggcct
24721 ccacgctgga agccatgctc agaaatgaca ccaacgacca gtcctttaat gactaccttt
24781 ccgccgccaa catgctatat cccatacccg ccaacgccac caacgtgccc atctccatcc
24841 catcgcgcaa ctgggcagca tttcgcggtt gggccttcac acgcttgaag acaaaggaaa
24901 ccccttccct gggatcaggc tacgaccctt actacaccta ctctggctcc ataccatacc
24961 ttgacggaac cttctatctt aatcacacct ttaagaaggt ggccattact tttgactctt
25021 ctgttagctg gccgggcaac gaccgcctgc ttactcccaa tgagtttgag attaagcgct
25081 cagttgacgg ggagggctat aacgtagctc agtgcaacat gacaaaggac tggttcctag
25141 tgcagatgtt ggccaactac aatattggct accagggctt ctacattcca gaaagctaca
25201 aagaccgcat gtactcgttc ttcagaaact tccagcccat gagccggcaa gtggtggacg
25261 atactaaata caaagattat cagcaggttg gaattatcca ccagcataac aactcaggct
25321 tcgtaggcta cctcgctccc accatgcgcg agggacaagc ttaccccgct aatgttccct
25381 acccactaat aggcaaaacc gcggttgata gtattaccca gaaaaagttt ctttgcgacc
25441 gcaccctgtg gcgcatcccc ttctccagta actttatgtc catgggtgcg ctcacagacc
25501 tgggccaaaa ccttctctac gcaaactccg cccacgcgct agacatgacc tttgaggtgg
25561 atcccatgga cgagcccacc cttctttatg ttttgtttga agtctttgac gtggtccgtg
25621 tgcaccagcc gcaccgcggc gtcatcgaga ccgtgtacct gcgcacgccc ttctcggccg
25681 gcaacgccac aacataaaga agcaagcaac atcaacaaca gctgccgcca tgggctccag
25741 tgagcaggaa ctgaaagcca ttgtcaaaga tcttggttgt gggccatatt ttttgggcac
25801 ctatgacaag cgcttcccag gctttgtttc cccacacaag ctcgcctgcg ccatagttaa
25861 cacggccggt cgcgagactg gggcgtaca ctggatggcc tttgcctgga acccgcgctc
25921 aaaaacatgc tacctctttg agccctttgg cttttctgac caacgtctca agcaggttta
25981 ccagtttgag tacgagtcac tcctgcgccg tagcgccatt gcctcttccc ccgaccgctg
26041 tataacgctg gaaaagtcca cccaaagcgt gcagggggccc aactcggccg cctgtggcct
26101 attctgctgc atgtttctcc acgcctttgc caactggccc caaactccca tggatcacaa
26161 ccccaccatg aaccttatta ccggggtacc caactccatg cttaacagtc cccaggtaca
26221 gcccaccctg cgccgcaacc aggaacagct ctacagcttc ctggagcgcc actcgcccta
26281 cttccgcagc cacagtgcgc aaattaggag cgccacttct ttttgtcact tgaaaaacat
26341 gtaaaaataa tgtactagga gacactttca ataaaggcaa atgtttttat ttgtacactc
26401 tcgggtgatt atttaccccc accccttgccg tctgcgccgt ttaaaaatca aaggggttct

FIG. 4I

26461 gccgcgcatc gctatgcgcc actggcaggg acacgttgcg atactggtgt ttagtgctcc
26521 acttaaactc aggcacaacc atccgcggca gctcggtgaa gttttcactc cacaggctgc
26581 gcaccatcac caacgcgttt agcaggtcgg gcgccgatat cttgaagtcg cagttggggc
26641 ctccgccctg cgcgcgcgag ttgcgataca cagggttaca gcactggaac actatcagcg
26701 ccgggtggtg cacgctggcc agcacgctct tgtcggagat cagatccgcg tccaggtcct
26761 ccgcgttgct cagggcgaac ggagtcaact ttggtagctg ccttcccaaa aagggtgcat
26821 gcccaggctt tgagttgcac tcgcaccgta gtggcatcag aaggtgaccg tgcccagtct
26881 gggcgttagg atacagcgcc tgcatgaaag ccttgatctg cttaaaagcc acctgagcct
26941 ttgcgccttc agagaagaac atgccgcaag acttgccgga aaactgattg gccggacagg
27001 ccgcgtcatg cacgcagcac cttgcgtcgg tgttggagat ctgcaccaca tttcggcccc
27061 accggttctt cacgatcttg gccttgctag actgctcctt cagcgcgcgc tgcccgtttt
27121 cgctcgtcac atccatttca atcacgtgct ccttatttat cataatgctc ccgtgtagac
27181 acttaagctc gccttcgatc tcagcgcagc ggtgcagcca caacgcgcag cccgtgggct
27241 cgtggtgctt gtaggttacc tctgcaaacg actgcaggta cgcctgcagg aatcgcccca
27301 tcatcgtcac aaaggtcttg ttgctggtga aggtcagctg caacccgcgg tgctcctcgt
27361 ttagccaggt cttgcatacg gccgccagag cttccacttg gtcaggcagt agcttgaagt
27421 ttgcctttag atcgttatcc acgtggtact tgtccatcaa cgcgcgcgca gcctccatgc
27481 ccttctccca cgcagacacg atcggcaggc tcagcgggtt tatcaccgtg ctttcacttt
27541 ccgcttcact ggactcttcc ttttcctctt gcatccgcat accccgcgcc actgggtcgt
27601 cttcattcag ccgccgcacc gtgcgcttac ctcccttgcc gtgcttgatt agcaccggtg
27661 ggttgctgaa acccaccatt tgtagcgcca catcttctct ttcttcctcg ctgtccacga
27721 tcacctctgg ggatggcggg cgctcgggct tgggagaggg gcgcttcttt ttctttttgg
27781 acgcaatggc caaatccgcc gtcgaggtcg atggccgcgg gctgggtgtg cgcggcacca
27841 gcgcatcttg tgacgagtct tcttcgtcct cggactcgag acgccgcctc agccgctttt
27901 ttgggggcgc gcggggaggc ggcggcgacg gcgacgggga cgagacgtcc tccatggttg
27961 gtggacgtcg cgccgcaccg cgtccgcgct cgggggtggt ttcgcgctgc tcctcttccc
28021 gactggccat ttccttctcc tataggcaga aaaagatcat ggagtcagtc gagaaggagg
28081 acagcctaac cgccccccttt gagttcgcca ccaccgcctc caccgatgcc gccaacgcgc
28141 ctaccacctt ccccgtcgag gcaccccccgc ttgaggagga ggaagtgatt atcgagcagg
28201 acccaggttt tgtaagcgaa gacgacgaag atcgctcagt accaacagag gataaaaagc
28261 aagaccagga cgacgcagag gcaaacgagg aacaagtcgg gcggggggac caaaggcatg
28321 gcgactacct agatgtggga gacgacgtgc tgttgaagca tctgcagcgc cagtgcgcca
28381 ttatctgcga cgcgttgcaa gagcgcagcg atgtgcccct cgcccatagcg gatgtcagcc
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28501 catgcgagcc caacccgcgc ctcaacttct accccgtatt tgccgtgcca gaggtgcttg
28561 ccacctatca catctttttc caaaactgca agatacccct atcctgccgt gccaaccgca
28621 gccgagcgga caagcagctg gccttgcggc agggcgctgt catacctgat atcgcctcgc
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28741 ctctgcaaca agaaaacagc gaaaatgaaa gtcactgtgg agtgctggtg gaacttgagg
28801 gtgacaacgc gcgcctagcc gtgctgaaac gcagcatcga ggtcacccac tttgcctacc
28861 cggcacttaa cctacccccc aaggttatga gcacagtcat gagcgagctg atcgtgcgcc
28921 gtgcacgacc cctggagagg gatgcaaact tgcaagaaca aaccgaggag ggcctacccg
28981 cagttggcga tgagcagctg gcgcgctggc ttgagacgcg cgagcctgcc gacttggagg
29041 agcgacgcaa gctaatgatg gccgcagtgc ttgttaccgt ggagcttgag tgcatgcagc
29101 ggttctttgc tgacccggag atgcagcgca agctagagga aacgttgcac tacacctttc
29161 gccagggcta cgtgcgccag gcctgcaaaa tttccaacgt ggagctctgc aacctggtct
29221 cctaccttgg aattttgcac gaaaaccgcc ttgggcaaaa cgtgcttcat tccacgctca
29281 agggcgaggc gcgccgcgac tacgtccgcg actgcgttta cttatttctg tgctacacct
29341 ggcaaacggc catgggcgtg tggcagcagt gcctggagga gcgcaacctg aaggagctgc
29401 agaagctgct aaagcaaaac ttgaaggacc tatggacggc cttcaacgag cgctccgtgg
29461 ccgcgcacct ggcggacatt atcttccccg aacgcctgct taaaaccctg caacagggtc
29521 tgccagactt caccagtcaa agcatgttgc aaaactttag gaactttatc ctagagcgtt
29581 caggaattct gcccgccacc tgctgtgcgc ttcctagcga ctttgtgccc attaagtacc
29641 gtgaatgccc tccgccgctt tggggtcact gctaccttct gcagctagcc aactaccttg
29701 cctaccactc cgacatcatg gaagacgtga gcggtgacgg cctactggag tgtcactgtc

FIG. 4J

```
29761 gctgcaacct atgcaccccg caccgctccc tggtctgcaa ttcacaactg cttagcgaaa
29821 gtcaaattat cggtaccttt gagctgcagg gtccctcgcc tgacgaaaag tccgcggctc
29881 cggggttgaa actcactccg ggctgtgga cgtcggctta ccttcgcaaa tttgtacctg
29941 aggactacca cgcccacgag attaggttct acgaagacca atcccgcccg ccaaatgcgg
30001 agcttaccgc ctgcgtcatt acccagggcc acatccttgg ccaattgcaa gccattaaca
30061 aagcccgcca agagtttctg ctacgaaagg gacgggggt ttacttggac ccccagtccg
30121 gcgaggagct caacccaatc cccccgccgc cgcagcccta tcagcagccg cgggcccttg
30181 cttcccagga tggcacccaa aaagaagctg cagctgccgc cgccgccacc cacggacgag
30241 gaggaatact gggacagtca ggcagaggag gttttggacg aggaggagga gatgatggaa
30301 gactgggaca gcctagacga ggaagcttcc gaggccgaag aggtgtcaga cgaaacaccg
30361 tcaccctcgg tcgcattccc ctcgccggcg ccccagaaat cggcaaccgt tcccagcatt
30421 gctacaacct ccgctcctca ggcgccgccg gcactgcccg ttcgccgacc caaccgtaga
30481 tgggacacca ctggaaccag ggccggtaag tctaagcagc cgccgccgtt agcccaagag
30541 caacaacagc gccaaggcta ccgctcgtgg cgcgtgcaca agaacgccat agttgcttgc
30601 ttgcaagact gtgggggcaa catctccttc gcccgccgct ttcttctcta ccatcacggc
30661 gtggccttcc cccgtaacat cctgcattac taccgtcatc tctacagccc ctactgcacc
30721 ggcggcagcg gcagcaacag cagcggccac gcagaagcaa aggcgaccgg atagcaagac
30781 tctgacaaag cccaagaaat ccacagcggc ggcagcagca ggaggaggag cactgcgtct
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30961 gcgctccctc acccgcagct gcctgtatca caaaagcgaa gatcagcttc ggcgcacgct
31021 ggaagacgcg gaggctctct tcagcaaata ctgcgcgctg actcttaagg actagtttcg
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31141 agcacctgtc gtcagcgcca ttatgagcaa ggaaattccc acgccctaca tgtggagtta
31201 ccagccacaa atgggacttg cggctggagc tgcccaagac tactcaaccc gaataaacta
31261 catgagcgcg ggaccccaca tgatatcccg ggtcaacgga atccgcgccc accgaaaccg
31321 aattctcctc gaacaggcgg ctattaccac cacacctcgt aataacctta atccccgtag
31381 ttggcccgct gccctggtgt accaggaaag tcccgctccc accactgtgg tacttcccag
31441 agacgcccag gccgaagttc agatgactaa ctcaggggcg cagcttgcgg gcggctttcg
31501 tcacagggtg cggtcgcccg ggcagggtat aactcacctg aaaatcagag ggcgaggtat
31561 tcagctcaac gacgagtcgg tgagctcctc tcttggtctc cgtccggacg ggacatttca
31621 gatcggcggc gctggccgct cttcatttac gccccgtcag gcgatcctaa ctctgcagac
31681 ctcgtcctcg gagccgcgct ccggaggcat tggaactcta caatttattg aggagttcgt
31741 gccttcggtt tacttcaacc ccttttctgg acctcccggc cactacccgg accagtttat
31801 tcccaacttt gacgcggtaa aagactcggc ggacggctac gactgaatga ccagtggaga
31861 ggcagagcaa ctgcgcctga cacacctcga ccactgccgc cgccacaagt gctttgcccg
31921 cggctccggt gagttttgtt actttgaatt gcccgaagag catatcgagg gcccggcgca
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32041 gcgcccccctg ctagtggagc gggagcgggg tccctgtgtt ctgaccgtgg tttgcaactg
32101 tcctaaccct ggattacatc aagatcttat tccattcaac taacaataaa cacacaataa
32161 attacttact taaaatcagt cagcaaatct ttgtccagct tattcagcat cacctccttt
32221 ccctcctccc aactctggta tttcagcagc cttttagctg cgaactttct ccaaagtcta
32281 aatgggatgt caaattcctc atgttcttgt ccctccgcac ccactatctt catattgttg
32341 cagatgaaac gcgccagacc gtctgaagac accttcaacc ctgtgtaccc atatgacacg
32401 gaaaccggcc ctccaactgt gcctttcctt acccctccct ttgtgtcgcc aaatgggttc
32461 caagaaagtc cccccggagt gctttctttg cgtctttcag aacctttggt tacctcacac
32521 ggcatgcttg cgctaaaaat gggcagcggc ctgtccctgg atcaggcagg caaccttaca
32581 tcaaatacaa tcactgtttc tcaaccgcta aaaaaaacaa agtccaatat aactttggaa
32641 acatccgcgc cccttacagt cagctcaggc gccctaacca tggccacaac ttcgcctttg
32701 gtggtctctg acaacactct taccatgcaa tcacaagcac cgctaaccgt gcaagactca
32761 aaacttagca ttgctaccaa agagccactt acagtgttag atggaaaact ggccctgcag
32821 acatcagccc ccctctctgc cactgataac aacgccctca ctatcactgc ctcacctcct
32881 cttactactg caaatggtag tctggctgtt accatggaaa acccacttta caacaacaat
32941 ggaaaacttg ggctcaaaat tggcggtcct ttgcaagtgg ccaccgactc acatgcacta
33001 acactaggta ctggtcaggg ggttgcagtt cataacaatt tgctacatac aaaagttaca
```

FIG. 4K

33061 ggcgcaatag ggtttgatac atctggcaac atggaactta aaactggaga tggcctctat
33121 gtggatagcg ccggtcctaa ccaaaaacta catattaatc taaataccac aaaaggcctt
33181 gcttttgaca acaccgcaat aacaattaac gctggaaaag ggttggaatt tgaaacagac
33241 tcctcaaacg gaaatcccat aaaaacaaaa attggatcag gcatacaata taataccaat
33301 ggagctatgg ttgcaaaact tggaacaggc ctcagttttg acagctccgg agccataaca
33361 atgggcagca taaacaatga cagacttact ctttggacaa caccagaccc atccccaaat
33421 tgcagaattg cttcagataa agactgcaag ctaactctgg cgctaacaaa atgtggcagt
33481 caaatttgg gcactgtttc agctttggca gtatcaggta atatggcctc catcaatgga
33541 actctaagca gtgtaaactt ggttcttaga tttgatgaca acggagtgct tatgtcaaat
33601 tcatcactgg acaaacagta ttggaacttt agaaacgggg actccactaa cggtcaacca
33661 tacacttatg ctgttgggtt tatgccaaac ctaaaagctt acccaaaaac tcaaagtaaa
33721 actgcaaaaa gtaatattgt tagccaggtg tatcttaatg gtgacaagtc taaaccattg
33781 cattttacta ttacgctaaa tggaacagat gaaaccaacc aagtaagcaa atactcaata
33841 tcattcagtt ggtcctggaa cagtggacaa tacactaatg acaaatttgc caccaattcc
33901 tataccttct cctacattgc ccaggaataa agaatcgtga acctgttgca tgttatgttt
33961 caacgtgttt atttttcaat tgcagaaaat ttcaagtcat ttttcattca gtagtatagc
34021 cccaccacca catagcttat actaatcacc gtaccttaat caaactcaca gaaccctagt
34081 attcaacctg ccacctccct cccaacacac agagtacaca gtcctttctc cccggctggc
34141 cttaaacagc atcatatcat gggtaacaga catattctta ggtgttatat tccacacggt
34201 ctcctgtcga gccaaacgct catcagtgat gttaataaac tccccgggca gctcgcttaa
34261 gttcatgtcg ctgtccagct gctgagccac aggctgctgt ccaacttgcg gttgctcaac
34321 gggcggcgaa ggagaagtcc acgcctacat gggggtagag tcataatcgt gcatcaggat
34381 agggcggtgg tgctgcagca gcgcgcgaat aaactgctgc cgccgccgct ccgtcctgca
34441 ggaatacaac atggcagtgg tctcctcagc gatgattcgc accgcccgca gcataaggcg
34501 ccttgtcctc cgggcacagc agcgcaccct gatctcactt aagtcagcac agtaactgca
34561 gcacagtacc acaatattgt ttaaaatccc acagtgcaag gcgctgtatc caaagctcat
34621 ggcggggacc acagaaccca cgtggccatc ataccacaag cgcaggtaga ttaagtggcg
34681 acccctcata aacacgctgg acataaacat tacctctttt ggcatgttgt aattcaccac
34741 ctcccggtac catataaacc tctgattaaa catggcgcca tccaccacca tcctaaacca
34801 gctggccaaa acctgcccgc cggctatgca ctgcagggaa ccgggactgg aacaatgaca
34861 gtggagagcc caggactcgt aaccatggat catcatgctc gtcatgatat caatgttggc
34921 acaacacagg cacacgtgca tacacttcct caggattaca agctcctccc gcgtcagaac
34981 catatcccag ggaacaaccc attcctgaat cagcgtaaat cccacactgc agggaagacc
35041 tcgcacgtaa ctcacgttgt gcattgtcaa agtgttacat tcgggcagca gcggatgatc
35101 ctccagtatg gtagcgcggg tttctgtctc aaaaggaggt agacgatccc tactgtacgg
35161 agtgcgccga gacaaccgag atcgtgttgg tcgtagtgtc atgccaaatg gaacgccgga
35221 cgtagtcata tttcctgaag caaaaccagg tgcgggcgtg acaaacagat ctgcgtctcc
35281 ggtctcgccg cttagatcgc tctgtgtagt agttgtagta tatccactct ctcaaagcat
35341 ccaggcgccc cctggcttcg ggttctatgt aaactccttc atgcgccgct gccctgataa
35401 catccaccac cgcagaataa gccacaccca gccaacctac acattcgttc tgcgagtcac
35461 acacgggagg agcgggaaga gctggaagaa ccatgttttt ttttttattc caaaagatta
35521 tccaaaacct caaaatgaag atctattaag tgaacgcgct cccctccggt ggcgtggtca
35581 aactctacag ccaaagaaca gataatggca tttgtaagat gttgcacaat ggcttccaaa
35641 aggcaaacgg ccctcacgtc caagtggacg taaaggctaa acccttcagg gtgaatctcc
35701 tctataaaca ttccagcacc ttcaaccatg cccaaataat tctcatctcg ccaccttctc
35761 aatatatctc taagcaaatc ccgaatatta agtccggcca ttgtaaaaat ctgctccaga
35821 gcgccctcca ccttcagcct caagcagcga atcatgattg caaaaattca ggttcctcac
35881 agacctgtat aagattcaaa agcggaacat taacaaaaat accgcgatcc cgtaggtccc
35941 ttcgcagggc cagctgaaca taatcgtgca ggtctgcacg gaccagcgcg gccacttccc
36001 cgccaggaac catgacaaaa gaacccacac tgattatgac acgcatactc ggagctatgc
36061 taaccagcgt agccccgatg taagcttgtt gcatgggcgg cgatataaaa tgcaaggtgc
36121 tgctcaaaaa atcaggcaaa gcctcgcgca aaaaagaaag cacatcgtag tcatgctcat
36181 gcagataaag gcaggtaagc tccggaacca ccacagaaaa agacaccatt tttctctcaa
36241 acatgtctgc gggtttctgc ataaacacaa aataaaataa caaaaaaaca tttaaacatt
36301 agaagcctgt cttacaacag gaaaaacaac ccttataagc ataagacgga ctacggccat

FIG. 4L

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36361 gccggcgtga ccgtaaaaaa actggtcacc gtgattaaaa agcaccaccg acagctcctc
36421 ggtcatgtcc ggagtcataa tgtaagactc ggtaaacaca tcaggttgat tcacatcggt
36481 cagtgctaaa aagcgaccga aatagcccgg gggaatacat acccgcaggc gtagagacaa
36541 cattacagcc cccataggag gtataacaaa attaatagga gagaaaaaca cataaacacc
36601 tgaaaaaccc tcctgcctag gcaaaatagc accctcccgc tccagaacaa catacagcgc
36661 ttccacagcg gcagccataa cagtcagcct taccagtaaa aaagaaaacc tattaaaaaa
36721 acaccactcg acacggcacc agctcaatca gtcacagtgt aaaaaagggc caagtgcaga
36781 gcgagtatat ataggactaa aaaatgacgt aacggttaaa gtccacaaaa aacacccaga
36841 aaaccgcacg cgaacctacg cccagaaacg aaagccaaaa aacccacaac ttcctcaaat
36901 cgtcacttcc gttttcccac gttacgtcac ttcccatttt aagaaaacta caattcccaa
36961 cacatacaag ttactccgcc ctaaaaccta cgtcacccgc ccgttccca cgccccgcgc
37021 cacgtcacaa actccacccc ctcattatca tattggcttc aatccaaaat aaggtatatt
37081 attgatgatg
```

FIG. 4M

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10                  30                  50
ATGGCGCCCATCACGGCCTACTCCCAACAGACGCGGGGCCTACTTGGTTGCATCATCACT
---------+---------+---------+---------+---------+---------+
MetAlaProIleThrAlaTyrSerGlnGlnThrArgGlyLeuLeuGlyCysIleIleThr
                            10                            20

        70                  90                 110
AGCCTTACAGGCCGGGACAAGAACCAGGTCGAGGGAGAGGTTCAGGTGGTTTCCACCGCA
---------+---------+---------+---------+---------+---------+
SerLeuThrGlyArgAspLysAsnGlnValGluGlyGluValGlnValValSerThrAla
                            30                            40

       130                 150                 170
ACACAATCCTTCCTGGCGACCTGCGTCAACGGCGTGTGTTGGACCGTTTACCATGGTGCT
---------+---------+---------+---------+---------+---------+
ThrGlnSerPheLeuAlaThrCysValAsnGlyValCysTrpThrValTyrHisGlyAla
                            50                            60

       190                 210                 230
GGCTCAAAGACCTTAGCCGGCCCAAAGGGGCCAATCACCCAGATGTACACTAATGTGGAC
---------+---------+---------+---------+---------+---------+
GlySerLysThrLeuAlaGlyProLysGlyProIleThrGlnMetTyrThrAsnValAsp
                            70                            80

       250                 270                 290
CAGGACCTCGTCGGCTGGCAGGCGCCCCCCGGGGCGCGTTCCTTGACACCATGCACCTGT
---------+---------+---------+---------+---------+---------+
GlnAspLeuValGlyTrpGlnAlaProProGlyAlaArgSerLeuThrProCysThrCys
                            90                           100

       310                 330                 350
GGCAGCTCAGACCTTTACTTGGTCACGAGACATGCTGACGTCATTCCGGTGCGCCGGCGG
---------+---------+---------+---------+---------+---------+
GlySerSerAspLeuTyrLeuValThrArgHisAlaAspValIleProValArgArgArg
                           110                           120

       370                 390                 410
GGCGACAGTAGGGGGAGCCTGCTCTCCCCCAGGCCTGTCTCCTACTTGAAGGGCTCTTCG
---------+---------+---------+---------+---------+---------+
GlyAspSerArgGlySerLeuLeuSerProArgProValSerTyrLeuLysGlySerSer
                           130                           140
```

FIG. 5A

```
         430                 450                 470
GGTGGTCCACTGCTCTGCCCTTCGGGGCACGCTGTGGGCATCTTCCGGGCTGCCGTATGC
---------+---------+---------+---------+---------+---------+
GlyGlyProLeuLeuCysProSerGlyHisAlaValGlyIlePheArgAlaAlaValCys
                         150                                160

         490                 510                 530
ACCCGGGGGGTTGCGAAGGCGGTGGACTTTGTGCCCGTAGAGTCCATGGAAACTACTATG
---------+---------+---------+---------+---------+---------+
ThrArgGlyValAlaLysAlaValAspPheValProValGluSerMetGluThrThrMet
                         170                                180

         550                 570                 590
CGGTCTCCGGTCTTCACGGACAACTCATCCCCCCCGGCCGTACCGCAGTCATTTCAAGTG
---------+---------+---------+---------+---------+---------+
ArgSerProValPheThrAspAsnSerSerProProAlaValProGlnSerPheGlnVal
                         190                                200

         610                 630                 650
GCCCACCTACACGCTCCCACTGGCAGCGGCAAGAGTACTAAAGTGCCGGCTGCATATGCA
---------+---------+---------+---------+---------+---------+
AlaHisLeuHisAlaProThrGlySerGlyLysSerThrLysValProAlaAlaTyrAla
                         210                                220

         670                 690                 710
GCCCAAGGGTACAAGGTGCTCGTCCTCAATCCGTCCGTTGCCGCTACCTTAGGGTTTGGG
---------+---------+---------+---------+---------+---------+
AlaGlnGlyTyrLysValLeuValLeuAsnProSerValAlaAlaThrLeuGlyPheGly
                         230                                240

         730                 750                 770
GCGTATATGTCTAAGGCACACGGTATTGACCCCAACATCAGAACTGGGGTAAGGACCATT
---------+---------+---------+---------+---------+---------+
AlaTyrMetSerLysAlaHisGlyIleAspProAsnIleArgThrGlyValArgThrIle
                         250                                260

         790                 810                 830
ACCACAGGCGCCCCCGTCACATACTCTACCTATGGCAAGTTTCTTGCCGATGGTGGTTGC
---------+---------+---------+---------+---------+---------+
ThrThrGlyAlaProValThrTyrSerThrTyrGlyLysPheLeuAlaAspGlyGlyCys
                         270                                280
```

FIG. 5B

```
       850                 870                 890
TCTGGGGGCGCTTATGACATCATAATATGTGATGAGTGCCATTCAACTGACTCGACTACA
---------+---------+---------+---------+---------+---------+
SerGlyGlyAlaTyrAspIleIleIleCysAspGluCysHisSerThrAspSerThrThr
                            290                           300

       910                 930                 950
ATCTTGGGCATCGGCACAGTCCTGGACCAAGCGGAGACGGCTGGAGCGCGGCTTGTCGTG
---------+---------+---------+---------+---------+---------+
IleLeuGlyIleGlyThrValLeuAspGlnAlaGluThrAlaGlyAlaArgLeuValVal
                            310                           320

       970                 990                1010
CTCGCCACCGCTACGCCTCCGGGATCGGTCACCGTGCCACACCCAAACATCGAGGAGGTG
---------+---------+---------+---------+---------+---------+
LeuAlaThrAlaThrProProGlySerValThrValProHisProAsnIleGluGluVal
                            330                           340

      1030                1050                1070
GCCCTGTCTAATACTGGAGAGATCCCCTTCTATGGCAAAGCCATCCCCATTGAAGCCATC
---------+---------+---------+---------+---------+---------+
AlaLeuSerAsnThrGlyGluIleProPheTyrGlyLysAlaIleProIleGluAlaIle
                            350                           360

      1090                1110                1130
AGGGGGGGAAGGCATCTCATTTTCTGTCATTCCAAGAAGAAGTGCGACGAGCTCGCCGCA
---------+---------+---------+---------+---------+---------+
ArgGlyGlyArgHisLeuIlePheCysHisSerLysLysLysCysAspGluLeuAlaAla
                            370                           380

      1150                1170                1190
AAGCTGTCAGGCCTCGGAATCAACGCTGTGGCGTATTACCGGGGGCTCGATGTGTCCGTC
---------+---------+---------+---------+---------+---------+
LysLeuSerGlyLeuGlyIleAsnAlaValAlaTyrTyrArgGlyLeuAspValSerVal
                            390                           400

      1210                1230                1250
ATACCAACTATCGGAGACGTCGTTGTCGTGGCAACAGACGCTCTGATGACGGGCTATACG
---------+---------+---------+---------+---------+---------+
IleProThrIleGlyAspValValValValAlaThrAspAlaLeuMetThrGlyTyrThr
                            410                           420
```

FIG. 5C

```
  1270                1290                1310
GGCGACTTTGACTCAGTGATCGACTGTAACACATGTGTCACCCAGACAGTCGACTTCAGC
---------+---------+---------+---------+---------+---------+
GlyAspPheAspSerValIleAspCysAsnThrCysValThrGlnThrValAspPheSer
                              430                           440

  1330                1350                1370
TTGGATCCCACCTTCACCATTGAGACGACGACCGTGCCTCAAGACGCAGTGTCGCGCTCG
---------+---------+---------+---------+---------+---------+
LeuAspProThrPheThrIleGluThrThrThrValProGlnAspAlaValSerArgSer
                              450                           460

  1390                1410                1430
CAGCGGCGGGGTAGGACTGGCAGGGGTAGGAGAGGCATCTACAGGTTTGTGACTCCGGGA
---------+---------+---------+---------+---------+---------+
GlnArgArgGlyArgThrGlyArgGlyArgArgGlyIleTyrArgPheValThrProGly
                              470                           480

  1450                1470                1490
GAACGGCCCTCGGGCATGTTCGATTCCTCGGTCCTGTGTGAGTGCTATGACGCGGGCTGT
---------+---------+---------+---------+---------+---------+
GluArgProSerGlyMetPheAspSerSerValLeuCysGluCysTyrAspAlaGlyCys
                              490                           500

  1510                1530                1550
GCTTGGTACGAGCTCACCCCCGCCGAGACCTCGGTTAGGTTGCGGGCCTACCTGAACACA
---------+---------+---------+---------+---------+---------+
AlaTrpTyrGluLeuThrProAlaGluThrSerValArgLeuArgAlaTyrLeuAsnThr
                              510                           520

  1570                1590                1610
CCAGGGTTGCCCGTTTGCCAGGACCACCTGGAGTTCTGGGAGAGTGTCTTCACAGGCCTC
---------+---------+---------+---------+---------+---------+
ProGlyLeuProValCysGlnAspHisLeuGluPheTrpGluSerValPheThrGlyLeu
                              530                           540

  1630                1650                1670
ACCCACATAGATGCACACTTCTTGTCCCAGACCAAGCAGGCAGGAGACAACTTCCCCTAC
---------+---------+---------+---------+---------+---------+
ThrHisIleAspAlaHisPheLeuSerGlnThrLysGlnAlaGlyAspAsnPheProTyr
                              550                           560
```

FIG. 5D

```
   1690                1710                1730
CTGGTAGCATACCAAGCCACGGTGTGCGCCAGGGCTCAGGCCCCACCTCCATCATGGGAT
---------+---------+---------+---------+---------+---------+
LeuValAlaTyrGlnAlaThrValCysAlaArgAlaGlnAlaProProProSerTrpAsp
                    570                                 580

   1750                1770                1790
CAAATGTGGAAGTGTCTCATACGGCTGAAACCTACGCTGCACGGGCCAACACCCTTGCTG
---------+---------+---------+---------+---------+---------+
GlnMetTrpLysCysLeuIleArgLeuLysProThrLeuHisGlyProThrProLeuLeu
                    590                                 600

   1810                1830                1850
TACAGGCTGGGAGCCGTCCAAAATGAGGTCACCCTCACCCACCCCATAACCAAATACATC
---------+---------+---------+---------+---------+---------+
TyrArgLeuGlyAlaValGlnAsnGluValThrLeuThrHisProIleThrLysTyrIle
                    610                                 620

   1870                1890                1910
ATGGCATGCATGTCGGCTGACCTGGAGGTCGTCACTAGCACCTGGGTGCTGGTGGGCGGA
---------+---------+---------+---------+---------+---------+
MetAlaCysMetSerAlaAspLeuGluValValThrSerThrTrpValLeuValGlyGly
                    630                                 640

   1930                1950                1970
GTCCTTGCAGCTCTGGCCGCGTATTGCCTGACAACAGGCAGTGTGGTCATTGTGGGTAGG
---------+---------+---------+---------+---------+---------+
ValLeuAlaAlaLeuAlaAlaTyrCysLeuThrThrGlySerValValIleValGlyArg
                    650                                 660

   1990                2010                2030
ATTATCTTGTCCGGGAGGCCGGCTATTGTTCCCGACAGGGAGTTTCTCTACCAGGAGTTC
---------+---------+---------+---------+---------+---------+
IleIleLeuSerGlyArgProAlaIleValProAspArgGluPheLeuTyrGlnGluPhe
                    670                                 680

   2050                2070                2090
GATGAAATGGAAGAGTGCGCCTCGCACCTCCCTTACATCGAGCAGGGAATGCAGCTCGCC
---------+---------+---------+---------+---------+---------+
AspGluMetGluGluCysAlaSerHisLeuProTyrIleGluGlnGlyMetGlnLeuAla
                    690                                 700
```

FIG. 5E

```
     2110                2130                2150
GAGCAATTCAAGCAGAAAGCGCTCGGGTTACTGCAAACAGCCACCAAACAAGCGGAGGCT
---------+---------+---------+---------+---------+---------+
GluGlnPheLysGlnLysAlaLeuGlyLeuLeuGlnThrAlaThrLysGlnAlaGluAla
                          710                             720

     2170                2190                2210
GCTGCTCCCGTGGTGGAGTCCAAGTGGCGAGCCCTTGAGACATTCTGGGCGAAGCACATG
---------+---------+---------+---------+---------+---------+
AlaAlaProValValGluSerLysTrpArgAlaLeuGluThrPheTrpAlaLysHisMet
                          730                             740

     2230                2250                2270
TGGAATTTCATCAGCGGGATACAGTACTTAGCAGGCTTATCCACTCTGCCTGGGAACCCC
---------+---------+---------+---------+---------+---------+
TrpAsnPheIleSerGlyIleGlnTyrLeuAlaGlyLeuSerThrLeuProGlyAsnPro
                          750                             760

     2290                2310                2330
GCAATAGCATCATTGATGGCATTCACAGCCTCTATCACCAGCCCGCTCACCACCCAAAGT
---------+---------+---------+---------+---------+---------+
AlaIleAlaSerLeuMetAlaPheThrAlaSerIleThrSerProLeuThrThrGlnSer
                          770                             780

     2350                2370                2390
ACCCTCCTGTTTAACATCTTGGGGGGGTGGGTGGCTGCCCAACTCGCCCCCCCCAGCGCC
---------+---------+---------+---------+---------+---------+
ThrLeuLeuPheAsnIleLeuGlyGlyTrpValAlaAlaGlnLeuAlaProProSerAla
                          790                             800

     2410                2430                2450
GCTTCGGCTTTCGTGGGCGCCGGCATCGCCGGTGCGGCTGTTGGCAGCATAGGCCTTGGG
---------+---------+---------+---------+---------+---------+
AlaSerAlaPheValGlyAlaGlyIleAlaGlyAlaAlaValGlySerIleGlyLeuGly
                          810                             820

     2470                2490                2510
AAGGTGCTTGTGGACATTCTGGCGGGTTATGGAGCAGGAGTGGCCGGCGCGCTCGTGGCC
---------+---------+---------+---------+---------+---------+
LysValLeuValAspIleLeuAlaGlyTyrGlyAlaGlyValAlaGlyAlaLeuValAla
                          830                             840
```

FIG. 5F

```
    2530                2550                2570
TTCAAGGTCATGAGCGGCGAGATGCCCTCCACCGAGGACCTGGTCAATCTACTTCCTGCC
---------+---------+---------+---------+---------+---------+
PheLysValMetSerGlyGluMetProSerThrGluAspLeuValAsnLeuLeuProAla
                        850                                860

    2590                2610                2630
ATCCTCTCTCCTGGCGCCCTGGTCGTCGGGGTCGTGTGTGCAGCAATACTGCGTCGACAC
---------+---------+---------+---------+---------+---------+
IleLeuSerProGlyAlaLeuValValGlyValValCysAlaAlaIleLeuArgArgHis
                        870                                880

    2650                2670                2690
GTGGGTCCGGGAGAGGGGGCTGTGCAGTGGATGAACCGGCTGATAGCGTTCGCCTCGCGG
---------+---------+---------+---------+---------+---------+
ValGlyProGlyGluGlyAlaValGlnTrpMetAsnArgLeuIleAlaPheAlaSerArg
                        890                                900

    2710                2730                2750
GGTAATCATGTTTCCCCCACGCACTATGTGCCTGAGAGCGACGCCGCAGCGCGTGTTACT
---------+---------+---------+---------+---------+---------+
GlyAsnHisValSerProThrHisTyrValProGluSerAspAlaAlaAlaArgValThr
                        910                                920

    2770                2790                2810
CAGATCCTCTCCAGCCTTACCATCACTCAGCTGCTGAAAAGGCTCCACCAGTGGATTAAT
---------+---------+---------+---------+---------+---------+
GlnIleLeuSerSerLeuThrIleThrGlnLeuLeuLysArgLeuHisGlnTrpIleAsn
                        930                                940

    2830                2850                2870
GAAGACTGCTCCACACCGTGTTCCGGCTCGTGGCTAAGGGATGTTTGGGACTGGATATGC
---------+---------+---------+---------+---------+---------+
GluAspCysSerThrProCysSerGlySerTrpLeuArgAspValTrpAspTrpIleCys
                        950                                960

    2890                2910                2930
ACGGTGTTGACTGACTTCAAGACCTGGCTCCAGTCCAAGCTCCTGCCGCAGCTACCGGGA
---------+---------+---------+---------+---------+---------+
ThrValLeuThrAspPheLysThrTrpLeuGlnSerLysLeuLeuProGlnLeuProGly
                        970                                980
```

FIG. 5G

```
      2950                2970                2990
GTCCCTTTTTTCTCGTGCCAACGCGGGTACAAGGGAGTCTGGCGGGGAGACGGCATCATG
---------+---------+---------+---------+---------+---------+
ValProPhePheSerCysGlnArgGlyTyrLysGlyValTrpArgGlyAspGlyIleMet
                              990                         1000

      3010                3030                3050
CAAACCACCTGCCCATGTGGAGCACAGATCACCGGACATGTCAAAAACGGTTCCATGAGG
---------+---------+---------+---------+---------+---------+
GlnThrThrCysProCysGlyAlaGlnIleThrGlyHisValLysAsnGlySerMetArg
                              1010                        1020

      3070                3090                3110
ATCGTCGGGCCTAAGACCTGCAGCAACACGTGGCATGGAACATTCCCCATCAACGCATAC
---------+---------+---------+---------+---------+---------+
IleValGlyProLysThrCysSerAsnThrTrpHisGlyThrPheProIleAsnAlaTyr
                              1030                        1040

      3130                3150                3170
ACCACGGGCCCCTGCACACCCTCTCCAGCGCCAAACTATTCTAGGGCGCTGTGGCGGGTG
---------+---------+---------+---------+---------+---------+
ThrThrGlyProCysThrProSerProAlaProAsnTyrSerArgAlaLeuTrpArgVal
                              1050                        1060

      3190                3210                3230
GCCGCTGAGGAGTACGTGGAGGTCACGCGGGTGGGGGATTTCCACTACGTGACGGGCATG
---------+---------+---------+---------+---------+---------+
AlaAlaGluGluTyrValGluValThrArgValGlyAspPheHisTyrValThrGlyMet
                              1070                        1080

      3250                3270                3290
ACCACTGACAACGTAAAGTGCCCATGCCAGGTTCCGGCTCCTGAATTCTTCACGGAGGTG
---------+---------+---------+---------+---------+---------+
ThrThrAspAsnValLysCysProCysGlnValProAlaProGluPhePheThrGluVal
                              1090                        1100

      3310                3330                3350
GACGGAGTGCGGTTGCACAGGTACGCTCCGGCGTGCAGGCCTCTCCTACGGGAGGAGGTT
---------+---------+---------+---------+---------+---------+
AspGlyValArgLeuHisArgTyrAlaProAlaCysArgProLeuLeuArgGluGluVal
                              1110                        1120
```

FIG. 5H

```
    3370                3390                3410
ACATTCCAGGTCGGGCTCAACCAATACCTGGTTGGGTCACAGCTACCATGCGAGCCCGAA
---------+---------+---------+---------+---------+---------+
ThrPheGlnValGlyLeuAsnGlnTyrLeuValGlySerGlnLeuProCysGluProGlu
                          1130                          1140

    3430                3450                3470
CCGGATGTAGCAGTGCTCACTTCCATGCTCACCGACCCCTCCCACATCACAGCAGAAACG
---------+---------+---------+---------+---------+---------+
ProAspValAlaValLeuThrSerMetLeuThrAspProSerHisIleThrAlaGluThr
                          1150                          1160

    3490                3510                3530
GCTAAGCGTAGGTTGGCCAGGGGGTCTCCCCCCTCCTTGGCCAGCTCTTCAGCTAGCCAG
---------+---------+---------+---------+---------+---------+
AlaLysArgArgLeuAlaArgGlySerProProSerLeuAlaSerSerSerAlaSerGln
                          1170                          1180

    3550                3570                3590
TTGTCTGCGCCTTCCTTGAAGGCGACATGCACTACCCACCATGTCTCTCCGGACGCTGAC
---------+---------+---------+---------+---------+---------+
LeuSerAlaProSerLeuLysAlaThrCysThrThrHisHisValSerProAspAlaAsp
                          1190                          1200

    3610                3630                3650
CTCATCGAGGCCAACCTCCTGTGGCGGCAGGAGATGGGCGGGAACATCACCCGCGTGGAG
---------+---------+---------+---------+---------+---------+
LeuIleGluAlaAsnLeuLeuTrpArgGlnGluMetGlyGlyAsnIleThrArgValGlu
                          1210                          1220

    3670                3690                3710
TCGGAGAACAAGGTGGTAGTCCTGGACTCTTTCGACCCGCTTCGAGCGGAGGAGGATGAG
---------+---------+---------+---------+---------+---------+
SerGluAsnLysValValValLeuAspSerPheAspProLeuArgAlaGluGluAspGlu
                          1230                          1240

    3730                3750                3770
AGGGAAGTATCCGTTCCGGCGGAGATCCTGCGGAAATCCAAGAAGTTCCCCGCAGCGATG
---------+---------+---------+---------+---------+---------+
ArgGluValSerValProAlaGluIleLeuArgLysSerLysLysPheProAlaAlaMet
                          1250                          1260
```

FIG. 5I

```
        3790                3810                3830
CCCATCTGGGCGCGCCCGGATTACAACCCTCCACTGTTAGAGTCCTGGAAGGACCCGGAC
---------+---------+---------+---------+---------+---------+
ProIleTrpAlaArgProAspTyrAsnProProLeuLeuGluSerTrpLysAspProAsp
                            1270                         1280

        3850                3870                3890
TACGTCCCTCCGGTGGTGCACGGGTGCCCGTTGCCACCTATCAAGGCCCCTCCAATACCA
---------+---------+---------+---------+---------+---------+
TyrValProProValValHisGlyCysProLeuProProIleLysAlaProProIlePro
                            1290                         1300

        3910                3930                3950
CCTCCACGGAGAAAGAGGACGGTTGTCCTAACAGAGTCCTCCGTGTCTTCTGCCTTAGCG
---------+---------+---------+---------+---------+---------+
ProProArgArgLysArgThrValValLeuThrGluSerSerValSerSerAlaLeuAla
                            1310                         1320

        3970                3990                4010
GAGCTCGCTACTAAGACCTTCGGCAGCTCCGAATCATCGGCCGTCGACAGCGGCACGGCG
---------+---------+---------+---------+---------+---------+
GluLeuAlaThrLysThrPheGlySerSerGluSerSerAlaValAspSerGlyThrAla
                            1330                         1340

        4030                4050                4070
ACCGCCCTTCCTGACCAGGCCTCCGACGACGGTGACAAAGGATCCGACGTTGAGTCGTAC
---------+---------+---------+---------+---------+---------+
ThrAlaLeuProAspGlnAlaSerAspAspGlyAspLysGlySerAspValGluSerTyr
                            1350                         1360

        4090                4110                4130
TCCTCCATGCCCCCCCTTGAGGGGGAACCGGGGGACCCCGATCTCAGTGACGGGTCTTGG
---------+---------+---------+---------+---------+---------+
SerSerMetProProLeuGluGlyGluProGlyAspProAspLeuSerAspGlySerTrp
                            1370                         1380

        4150                4170                4190
TCTACCGTGAGCGAGGAAGCTAGTGAGGATGTCGTCTGCTGCTCAATGTCCTACACATGG
---------+---------+---------+---------+---------+---------+
SerThrValSerGluGluAlaSerGluAspValValCysCysSerMetSerTyrThrTrp
                            1390                         1400
```

FIG. 5J

```
4210                4230                4250
ACAGGCGCCTTGATCACGCCATGCGCTGCGGAGGAAAGCAAGCTGCCCATCAACGCGTTG
---------+---------+---------+---------+---------+---------+
ThrGlyAlaLeuIleThrProCysAlaAlaGluGluSerLysLeuProIleAsnAlaLeu
                    1410                                1420

4270                4290                4310
AGCAACTCTTTGCTGCGCCACCATAACATGGTTTATGCCACAACATCTCGCAGCGCAGGC
---------+---------+---------+---------+---------+---------+
SerAsnSerLeuLeuArgHisHisAsnMetValTyrAlaThrThrSerArgSerAlaGly
                    1430                                1440

4330                4350                4370
CTGCGGCAGAAGAAGGTCACCTTTGACAGACTGCAAGTCCTGGACGACCACTACCGGGAC
---------+---------+---------+---------+---------+---------+
LeuArgGlnLysLysValThrPheAspArgLeuGlnValLeuAspAspHisTyrArgAsp
                    1450                                1460

4390                4410                4430
GTGCTCAAGGAGATGAAGGCGAAGGCGTCCACAGTTAAGGCTAAACTCCTATCCGTAGAG
---------+---------+---------+---------+---------+---------+
ValLeuLysGluMetLysAlaLysAlaSerThrValLysAlaLysLeuLeuSerValGlu
                    1470                                1480

4450                4470                4490
GAAGCCTGCAAGCTGACGCCCCCACATTCGGCCAAATCCAAGTTTGGCTATGGGGCAAAG
---------+---------+---------+---------+---------+---------+
GluAlaCysLysLeuThrProProHisSerAlaLysSerLysPheGlyTyrGlyAlaLys
                    1490                                1500

4510                4530                4550
GACGTCCGGAACCTATCCAGCAAGGCCGTTAACCACATCCACTCCGTGTGGAAGGACTTG
---------+---------+---------+---------+---------+---------+
AspValArgAsnLeuSerSerLysAlaValAsnHisIleHisSerValTrpLysAspLeu
                    1510                                1520

4570                4590                4610
CTGGAAGACACTGTGACACCAATTGACACCACCATCATGGCAAAAAATGAGGTTTTCTGT
---------+---------+---------+---------+---------+---------+
LeuGluAspThrValThrProIleAspThrThrIleMetAlaLysAsnGluValPheCys
                    1530                                1540
```

FIG. 5K

```
    4630                4650                4670
GTCCAACCAGAGAAAGGAGGCCGTAAGCCAGCCCGCCTTATCGTATTCCCAGATCTGGGA
---------+---------+---------+---------+---------+---------+
ValGlnProGluLysGlyGlyArgLysProAlaArgLeuIleValPheProAspLeuGly
                    1550                          1560

    4690                4710                4730
GTCCGTGTATGCGAGAAGATGGCCCTCTATGATGTGGTCTCCACCCTTCCTCAGGTCGTG
---------+---------+---------+---------+---------+---------+
ValArgValCysGluLysMetAlaLeuTyrAspValValSerThrLeuProGlnValVal
                    1570                          1580

    4750                4770                4790
ATGGGCTCCTCATACGGATTCCAGTACTCTCCTGGGCAGCGAGTCGAGTTCCTGGTGAAT
---------+---------+---------+---------+---------+---------+
MetGlySerSerTyrGlyPheGlnTyrSerProGlyGlnArgValGluPheLeuValAsn
                    1590                          1600

    4810                4830                4850
ACCTGGAAATCAAAGAAAAACCCCATGGGCTTTTCATATGACACTCGCTGTTTCGACTCA
---------+---------+---------+---------+---------+---------+
ThrTrpLysSerLysLysAsnProMetGlyPheSerTyrAspThrArgCysPheAspSer
                    1610                          1620

    4870                4890                4910
ACGGTCACCGAGAACGACATCCGTGTTGAGGAGTCAATTTACCAATGTTGTGACTTGGCC
---------+---------+---------+---------+---------+---------+
ThrValThrGluAsnAspIleArgValGluGluSerIleTyrGlnCysCysAspLeuAla
                    1630                          1640

    4930                4950                4970
CCCGAAGCCAGACAGGCCATAAAATCGCTCACAGAGCGGCTTTATATCGGGGGTCCTCTG
---------+---------+---------+---------+---------+---------+
ProGluAlaArgGlnAlaIleLysSerLeuThrGluArgLeuTyrIleGlyGlyProLeu
                    1650                          1660

    4990                5010                5030
ACTAATTCAAAAGGGCAGAACTGCGGTTATCGCCGGTGCCGCGCGAGCGGCGTGCTGACG
---------+---------+---------+---------+---------+---------+
ThrAsnSerLysGlyGlnAsnCysGlyTyrArgArgCysArgAlaSerGlyValLeuThr
                    1670                          1680
```

FIG. 5L

```
    5050                5070                5090
ACTAGCTGCGGTAACACCCTCACATGTTACTTGAAGGCCTCTGCAGCCTGTCGAGCTGCG
---------+---------+---------+---------+---------+---------+
ThrSerCysGlyAsnThrLeuThrCysTyrLeuLysAlaSerAlaAlaCysArgAlaAla
                        1690                          1700

    5110                5130                5150
AAGCTCCAGGACTGCACGATGCTCGTGAACGGAGACGACCTTGTCGTTATCTGTGAAAGC
---------+---------+---------+---------+---------+---------+
LysLeuGlnAspCysThrMetLeuValAsnGlyAspAspLeuValValIleCysGluSer
                        1710                          1720

    5170                5190                5210
GCGGGAACCCAAGAGGACGCGGCGAGCCTACGAGTCTTCACGGAGGCTATGACTAGGTAC
---------+---------+---------+---------+---------+---------+
AlaGlyThrGlnGluAspAlaAlaSerLeuArgValPheThrGluAlaMetThrArgTyr
                        1730                          1740

    5230                5250                5270
TCTGCCCCCCCCGGGGACCCGCCCCAACCAGAATACGACTTGGAGCTGATAACATCATGT
---------+---------+---------+---------+---------+---------+
SerAlaProProGlyAspProProGlnProGluTyrAspLeuGluLeuIleThrSerCys
                        1750                          1760

    5290                5310                5330
TCCTCCAATGTGTCGGTCGCCCACGATGCATCAGGCAAAAGGGTGTACTACCTCACCCGT
---------+---------+---------+---------+---------+---------+
SerSerAsnValSerValAlaHisAspAlaSerGlyLysArgValTyrTyrLeuThrArg
                        1770                          1780

    5350                5370                5390
GATCCCACCACCCCCCTCGCACGGGCTGCGTGGGAAACAGCTAGACACACTCCAGTTAAC
---------+---------+---------+---------+---------+---------+
AspProThrThrProLeuAlaArgAlaAlaTrpGluThrAlaArgHisThrProValAsn
                        1790                          1800

    5410                5430                5450
TCCTGGCTAGGCAACATTATCATGTATGCGCCCACTTTGTGGGCAAGGATGATTCTGATG
---------+---------+---------+---------+---------+---------+
SerTrpLeuGlyAsnIleIleMetTyrAlaProThrLeuTrpAlaArgMetIleLeuMet
                        1810                          1820
```

FIG. 5M

```
     5470                 5490                 5510
ACTCACTTCTTCTCCATCCTTCTAGCACAGGAGCAACTTGAAAAAGCCCTGGACTGCCAG
---------+---------+---------+---------+---------+---------+
ThrHisPhePheSerIleLeuLeuAlaGlnGluGlnLeuGluLysAlaLeuAspCysGln
                          1830                           1840

     5530                 5550                 5570
ATCTACGGGGCCTGTTACTCCATTGAGCCACTTGACCTACCTCAGATCATTGAACGACTC
---------+---------+---------+---------+---------+---------+
IleTyrGlyAlaCysTyrSerIleGluProLeuAspLeuProGlnIleIleGluArgLeu
                          1850                           1860

     5590                 5610                 5630
CATGGCCTTAGCGCATTTTCACTCCATAGTTACTCTCCAGGTGAGATCAATAGGGTGGCT
---------+---------+---------+---------+---------+---------+
HisGlyLeuSerAlaPheSerLeuHisSerTyrSerProGlyGluIleAsnArgValAla
                          1870                           1880

     5650                 5670                 5690
TCATGCCTCAGGAAACTTGGGGTACCACCCTTGCGAGTCTGGAGACATCGGGCCAGGAGC
---------+---------+---------+---------+---------+---------+
SerCysLeuArgLysLeuGlyValProProLeuArgValTrpArgHisArgAlaArgSer
                          1890                           1900

     5710                 5730                 5750
GTCCGCGCTAGGCTACTGTCCCAGGGGGGGAGGGCCGCCACTTGTGGCAAGTACCTCTTC
---------+---------+---------+---------+---------+---------+
ValArgAlaArgLeuLeuSerGlnGlyGlyArgAlaAlaThrCysGlyLysTyrLeuPhe
                          1910                           1920

     5770                 5790                 5810
AACTGGGCAGTGAAGACCAAACTCAAACTCACTCCAATCCCGGCTGCGTCCCAGCTGGAC
---------+---------+---------+---------+---------+---------+
AsnTrpAlaValLysThrLysLeuLysLeuThrProIleProAlaAlaSerGlnLeuAsp
                          1930                           1940

     5830                 5850                 5870
TTGTCCGGCTGGTTCGTTGCTGGTTACAGCGGGGGAGACATATATCACAGCCTGTCTCGT
---------+---------+---------+---------+---------+---------+
LeuSerGlyTrpPheValAlaGlyTyrSerGlyGlyAspIleTyrHisSerLeuSerArg
                          1950                           1960
```

FIG. 5N

```
     5890                5910                5930
GCCCGACCCCGCTGGTTCATGCTGTGCCTACTCCTACTTTCTGTAGGGGTAGGCATCTAC
---------+---------+---------+---------+---------+---------+
AlaArgProArgTrpPheMetLeuCysLeuLeuLeuLeuSerValGlyValGlyIleTyr
                         1970                              1980

     5950 5955
CTGCTCCCCAACCGA   (SEQ. ID. NO. 5)
---------+-----
LeuLeuProAsnArg   (SEQ. ID. NO. 6)
          1985
```

FIG. 5O

```
   1 TCGCGCGTTT CGGTGATGAC GGTGAAAACC TCTGACACAT GCAGCTCCCG
  51 GAGACGGTCA CAGCTTGTCT GTAAGCGGAT GCCGGGAGCA GACAAGCCCG
 101 TCAGGGCGCG TCAGCGGGTG TTGGCGGGTG TCGGGGCTGG CTTAACTATG
 151 CGGCATCAGA GCAGATTGTA CTGAGAGTGC ACCATATGCG GTGTGAAATA
 201 CCGCACAGAT GCGTAAGGAG AAAATACCGC ATCAGATTGG CTATTGGCCA
 251 TTGCATACGT TGTATCCATA TCATAATATG TACATTTATA TTGGCTCATG
 301 TCCAACATTA CCGCCATGTT GACATTGATT ATTGACTAGT TATTAATAGT
 351 AATCAATTAC GGGGTCATTA GTTCATAGCC CATATATGGA GTTCCGCGTT
 401 ACATAACTTA CGGTAAATGG CCCGCCTGGC TGACCGCCCA ACGACCCCCG
 451 CCCATTGACG TCAATAATGA CGTATGTTCC CATAGTAACG CCAATAGGGA
 501 CTTTCCATTG ACGTCAATGG GTGGAGTATT TACGGTAAAC TGCCCACTTG
 551 GCAGTACATC AAGTGTATCA TATGCCAAGT ACGCCCCCTA TTGACGTCAA
 601 TGACGGTAAA TGGCCCGCCT GGCATTATGC CCAGTACATG ACCTTATGGG
 651 ACTTTCCTAC TTGGCAGTAC ATCTACGTAT TAGTCATCGC TATTACCATG
 701 GTGATGCGGT TTTGGCAGTA CATCAATGGG CGTGGATAGC GGTTTGACTC
 751 ACGGGGATTT CCAAGTCTCC ACCCCATTGA CGTCAATGGG AGTTTGTTTT
 801 GGCACCAAAA TCAACGGGAC TTTCCAAAAT GTCGTAACAA CTCCGCCCCA
 851 TTGACGCAAA TGGGCGGTAG GCGTGTACGG TGGGAGGTCT ATATAAGCAG
 901 AGCTCGTTTA GTGAACCGTC AGATCGCCTG GAGACGCCAT CCACGCTGTT
 951 TTGACCTCCA TAGAAGACAC CGGGACCGAT CCAGCCTCCG CGGCCGGGAA
1001 CGGTGCATTG GAACGCGGAT TCCCCGTGCC AAGAGTGACG TAAGTACCGC
1051 CTATAGACTC TATAGGCACA CCCCTTTGGC TCTTATGCAT GCTATACTGT
1101 TTTTGGCTTG GGGCCTATAC ACCCCCGCTT CCTTATGCTA TAGGTGATGG
1151 TATAGCTTAG CCTATAGGTG TGGGTTATTG ACCATTATTG ACCACTCCCC
1201 TATTGGTGAC GATACTTTCC ATTACTAATC CATAACATGG CTCTTTGCCA
1251 CAACTATCTC TATTGGCTAT ATGCCAATAC TCTGTCCTTC AGAGACTGAC
1301 ACGGACTCTG TATTTTTACA GGATGGGGTC CCATTTATTA TTTACAAATT
1351 CACATATACA ACAACGCCGT CCCCCGTGCC CGCAGTTTTT ATTAAACATA
1401 GCGTGGGATC TCCACGCGAA TCTCGGGTAC GTGTTCCGGA CATGGGCTCT
1451 TCTCCGGTAG CGGCGGAGCT TCCACATCCG AGCCCTGGTC CCATGCCTCC
1501 AGCGGCTCAT GGTCGCTCGG CAGCTCCTTG CTCCTAACAG TGGAGGCCAG
1551 ACTTAGGCAC AGCACAATGC CCACCACCAC CAGTGTGCCG CACAAGGCCG
1601 TGGCGGTAGG GTATGTGTCT GAAAATGAGC GTGGAGATTG GGCTCGCACG
1651 GCTGACGCAG ATGGAAGACT TAAGGCAGCG GCAGAAGAAG ATGCAGGCAG
1701 CTGAGTTGTT GTATTCTGAT AAGAGTCAGA GGTAACTCCC GTTGCGGTGC
1751 TGTTAACGGT GGAGGGCAGT GTAGTCTGAG CAGTACTCGT TGCTGCCGCG
1801 CGCGCCACCA GACATAATAG CTGACAGACT AACAGACTGT TCCTTTCCAT
1851 GGGTCTTTTC TGCAGTCACC GTCCTTAGAT CTAGGTACCA GATATCAGAA
1901 TTCAGTCGAC AGCGGCCGCG ATCTGCTGTG CCTTCTAGTT GCCAGCCATC
1951 TGTTGTTTGC CCCTCCCCCG TGCCTTCCTT GACCCTGGAA GGTGCCACTC
2001 CCACTGTCCT TTCCTAATAA AATGAGGAAA TTGCATCGCA TTGTCTGAGT
2051 AGGTGTCATT CTATTCTGGG GGGTGGGGTG GGGCAGGACA GCAAGGGGGA
```

FIG. 6A

2101 GGATTGGGAA GACAATAGCA GGCATGCTGG GGATGCGGTG GGCTCTATGG
2151 CCGCTGCGGC CAGGTGCTGA AGAATTGACC CGGTTCCTCC TGGGCCAGAA
2201 AGAAGCAGGC ACATCCCCTT CTCTGTGACA CACCCTGTCC ACGCCCCTGG
2251 TTCTTAGTTC CAGCCCCACT CATAGGACAC TCATAGCTCA GGAGGGCTCC
2301 GCCTTCAATC CCACCCGCTA AAGTACTTGG AGCGGTCTCT CCCTCCCTCA
2351 TCAGCCCACC AAACCAAACC TAGCCTCCAA GAGTGGGAAG AAATTAAAGC
2401 AAGATAGGCT ATTAAGTGCA GAGGGAGAGA AAATGCCTCC AACATGTGAG
2451 GAAGTAATGA GAGAAATCAT AGAATTTCTT CCGCTTCCTC GCTCACTGAC
2501 TCGCTGCGCT CGGTCGTTCG GCTGCGGCGA GCGGTATCAG CTCACTCAAA
2551 GGCGGTAATA CGGTTATCCA CAGAATCAGG GGATAACGCA GGAAAGAACA
2601 TGTGAGCAAA AGGCCAGCAA AAGGCCAGGA ACCGTAAAAA GGCCGCGTTG
2651 CTGGCGTTTT TCCATAGGCT CCGCCCCCCT GACGAGCATC ACAAAAATCG
2701 ACGCTCAAGT CAGAGGTGGC GAAACCCGAC AGGACTATAA AGATACCAGG
2751 CGTTTCCCCC TGGAAGCTCC CTCGTGCGCT CTCCTGTTCC GACCCTGCCG
2801 CTTACCGGAT ACCTGTCCGC CTTTCTCCCT TCGGGAAGCG TGGCGCTTTC
2851 TCATAGCTCA CGCTGTAGGT ATCTCAGTTC GGTGTAGGTC GTTCGCTCCA
2901 AGCTGGGCTG TGTGCACGAA CCCCCCGTTC AGCCCGACCG CTGCGCCTTA
2951 TCCGGTAACT ATCGTCTTGA GTCCAACCCG GTAAGACACG ACTTATCGCC
3001 ACTGGCAGCA GCCACTGGTA ACAGGATTAG CAGAGCGAGG TATGTAGGCG
3051 GTGCTACAGA GTTCTTGAAG TGGTGGCCTA ACTACGGCTA CACTAGAAGA
3101 ACAGTATTTG GTATCTGCGC TCTGCTGAAG CCAGTTACCT TCGGAAAAAG
3151 AGTTGGTAGC TCTTGATCCG GCAAACAAAC CACCGCTGGT AGCGGTGGTT
3201 TTTTTGTTTG CAAGCAGCAG ATTACGCGCA GAAAAAAAGG ATCTCAAGAA
3251 GATCCTTTGA TCTTTTCTAC GGGGTCTGAC GCTCAGTGGA ACGAAAACTC
3301 ACGTTAAGGG ATTTTGGTCA TGAGATTATC AAAAAGGATC TTCACCTAGA
3351 TCCTTTTAAA TTAAAAATGA AGTTTTAAAT CAATCTAAAG TATATATGAG
3401 TAAACTTGGT CTGACAGTTA CCAATGCTTA ATCAGTGAGG CACCTATCTC
3451 AGCGATCTGT CTATTTCGTT CATCCATAGT TGCCTGACTC GGGGGGGGGG
3501 GGCGCTGAGG TCTGCCTCGT GAAGAAGGTG TTGCTGACTC ATACCAGGCC
3551 TGAATCGCCC CATCATCCAG CCAGAAAGTG AGGGAGCCAC GGTTGATGAG
3601 AGCTTTGTTG TAGGTGGACC AGTTGGTGAT TTTGAACTTT TGCTTTGCCA
3651 CGGAACGGTC TGCGTTGTCG GGAAGATGCG TGATCTGATC CTTCAACTCA
3701 GCAAAAGTTC GATTTATTCA ACAAAGCCGC CGTCCCGTCA AGTCAGCGTA
3751 ATGCTCTGCC AGTGTTACAA CCAATTAACC AATTCTGATT AGAAAAACTC
3801 ATCGAGCATC AAATGAAACT GCAATTTATT CATATCAGGA TTATCAATAC
3851 CATATTTTTG AAAAAGCCGT TTCTGTAATG AAGGAGAAAA CTCACCGAGG
3901 CAGTTCCATA GGATGGCAAG ATCCTGGTAT CGGTCTGCGA TTCCGACTCG
3951 TCCAACATCA ATACAACCTA TTAATTTCCC CTCGTCAAAA ATAAGGTTAT
4001 CAAGTGAGAA ATCACCATGA GTGACGACTG AATCCGGTGA GAATGGCAAA
4051 AGCTTATGCA TTTCTTTCCA GACTTGTTCA ACAGGCCAGC CATTACGCTC
4101 GTCATCAAAA TCACTCGCAT CAACCAAACC GTTATTCATT CGTGATTGCG
4151 CCTGAGCGAG ACGAAATACG CGATCGCTGT TAAAAGGACA ATTACAAACA

FIG. 6B

```
4201  GGAATCGAAT GCAACCGGCG CAGGAACACT GCCAGCGCAT CAACAATATT
4251  TTCACCTGAA TCAGGATATT CTTCTAATAC CTGGAATGCT GTTTTCCCGG
4301  GGATCGCAGT GGTGAGTAAC CATGCATCAT CAGGAGTACG GATAAAATGC
4351  TTGATGGTCG GAAGAGGCAT AAATTCCGTC AGCCAGTTTA GTCTGACCAT
4401  CTCATCTGTA ACATCATTGG CAACGCTACC TTTGCCATGT TTCAGAAACA
4451  ACTCTGGCGC ATCGGGCTTC CCATACAATC GATAGATTGT CGCACCTGAT
4501  TGCCCGACAT TATCGCGAGC CCATTTATAC CCATATAAAT CAGCATCCAT
4551  GTTGGAATTT AATCGCGGCC TCGAGCAAGA CGTTTCCCGT TGAATATGGC
4601  TCATAACACC CCTTGTATTA CTGTTTATGT AAGCAGACAG TTTTATTGTT
4651  CATGATGATA TATTTTTATC TTGTGCAATG TAACATCAGA GATTTTGAGA
4701  CACAACGTGG CTTTCCCCCC CCCCCCATTA TTGAAGCATT TATCAGGGTT
4751  ATTGTCTCAT GAGCGGATAC ATATTTGAAT GTATTTAGAA AAATAAACAA
4801  ATAGGGGTTC CGCGCACATT TCCCCGAAAA GTGCCACCTG ACGTCTAAGA
4851  AACCATTATT ATCATGACAT TAACCTATAA AAATAGGCGT ATCACGAGGC
4901  CCTTTCGTC
```

FIG. 6C

1 CATCATCAAT AATATACCTT ATTTTGGATT GAAGCCAATA TGATAATGAG GGGGTGGAGT
61 TTGTGACGTG GCGCGGGGCG TGGGAACGGG GCGGGTGACG TAGTAGTGTG GCGGAAGTGT
121 GATGTTGTAA GTGTGGCGGA ACACATGTAA GCGCCGGATG TGGTAAAAGT GACGTTTTTG
181 GTGTGCGCCG GTGTACACGG GAAGTGACAA TTTTCGCGCG GTTTTAGGCG GATGTTGTAG
241 TAAATTTGGG CGTAACCAAG TAATATTTGG CCATTTTCGC GGGAAAACTG AATAAGAGGA
301 AGTGAAATCT GAATAATTCT GTGTTACTCA TAGCGCGTAA TATTTGTCTA GGGCCGCGGG
361 GACTTTGACC GTTTACGTGG AGACTCGCCC AGGTGTTTTT CTCAGGTGTT TTCCGCGTTC
421 CGGGTCAAAG TTGGCGTTTT ATTATTATAG TCAGCTGACG CGCAGTGTAT TTATACCCGG
481 TGAGTTCCTC AAGAGGCCAC TCTTGAGTGC CAGCGAGTAG AGTTTTCTCC TCCGAGCCGC
541 TCCGACACCG GGACTGAAAA TGAGACATAT TATCTGCCAC GGAGGTGTTA TTACCGAAGA
601 AATGGCCGCC AGTCTTTTGG ACCAGCTGAT CGAAGAGGTA CTGGCTGATA ATCTTCCACC
661 TCCTAGCCAT TTTGAACCAC CTACCCTTCA CGAACTGTAT GATTTAGACG TGACGGCCCC
721 CGAAGATCCC AACGAGGAGG CGGTTTCGCA GATTTTTCCC GAGTCTGTAA TGTTGGCGGT
781 GCAGGAAGGG ATTGACTTAT TCACTTTTCC GCCGGCGCCC GGTTCTCCGG AGCCGCCTCA
841 CCTTTCCCGG CAGCCCGAGC AGCCGGAGCA GAGAGCCTTG GGTCCGGTTT CTATGCCAAA
901 CCTTGTGCCG GAGGTGATCG ATCTTACCTG CCACGAGGCT GGCTTTCCAC CCAGTGACGA
961 CGAGGATGAA GAGGGTGAGG AGTTTGTGTT AGATTATGTG GAGCACCCCG GGCACGGTTG
1021 CAGGTCTTGT CATTATCACC GGAGGAATAC GGGGGACCCA GATATTATGT GTTCGCTTTG
1081 CTATATGAGG ACCTGTGGCA TGTTTGTCTA CAGTAAGTGA AAAATTATGG GCAGTGGGTG
1141 ATAGAGTGGT GGGTTTGGTG TGGTAATTTT TTTTTTAATT TTTACAGTTT TGTGGTTTAA
1201 AGAATTTTGT ATTGTGATTT TTTAAAAGGT CCTGTGTCTG AACCTGAGCC TGAGCCCGAG
1261 CCAGAACCGG AGCCTGCAAG ACCTACCCGG CGTCCTAAAT TGGTGCCTGC TATCCTGAGA
1321 CGCCCGACAT CACCTGTGTC TAGAGAATGC AATAGTAGTA CGGATAGCTG TGACTCCGGT
1381 CCTTCTAACA CACCTCCTGA GATACACCCG GTGGTCCCGC TGTGCCCCAT TAAACCAGTT
1441 GCCGTGAGAG TTGGTGGGCG TCGCCAGGCT GTGGAATGTA TCGAGGACTT GCTTAACGAG
1501 TCTGGGCAAC CTTTGGACTT GAGCTGTAAA CGCCCCAGGC CATAAGGTGT AAACCTGTGA
1561 TTGCGTGTGT GGTTAACGCC TTTGTTTGCT GAATGAGTTG ATGTAAGTTT AATAAAGGGT
1621 GAGATAATGT TTAACTTGCA TGGCGTGTTA AATGGGGCGG GGCTTAAAGG GTATATAATG
1681 CGCCGTGGGC TAATCTTGGT TACATCTGAC CTCATGGAGG CTTGGGAGTG TTTGGAAGAT
1741 TTTTCTGCTG TGCGTAACTT GCTGGAACAG AGCTCTAACA GTACCTCTTG GTTTTGGAGG
1801 TTTCTGTGGG GCTCCTCCCA GGCAAAGTTA GTCTGCAGAA TTAAGGAGGA TTACAAGTGG
1861 GAATTTGAAG AGCTTTTGAA ATCCTGTGGT GAGCTGTTTG ATTCTTTGAA TCTGGGTCAC
1921 CAGGCGCTTT TCCAAGAGAA GGTCATCAAG ACTTTGGATT TTTCCACACC GGGGCGCGCT
1981 GCGGCTGCTG TTGCTTTTTT GAGTTTTATA AAGGATAAAT GGAGCGAAGA AACCCATCTG
2041 AGCGGGGGGT ACCTGCTGGA TTTTCTGGCC ATGCATCTGT GGAGAGCGGT GGTGAGACAC
2101 AAGAATCGCC TGCTACTGTT GTCTTCCGTC CGCCCGGCAA TAATACCGAC GGAGGAGCAA
2161 CAGCAGGAGG AAGCCAGGCG GCGGCGGCGG CAGGAGCAGA GCCCATGGAA CCCGAGAGCC
2221 GGCCTGGACC CTCGGGAATG AATGTTGTAC AGGTGGCTGA ACTGTTTCCA GAACTGAGAC
2281 GCATTTTAAC CATTAACGAG GATGGGCAGG GGCTAAAGGG GGTAAAGAAG GAGCGGGGGG
2341 CTTCTGAGGC TACAGAGGAG GCTAGGAATC TAACTTTTAG CTTAATGACC AGACACCGTC
2401 CTGAGTGTGT TACTTTTCAG CAGATTAAGG ATAATTGCGC TAATGAGCTT GATCTGCTGG
2461 CGCAGAAGTA TTCCATAGAG CAGCTGACCA CTTACTGGCT GCAGCCAGGG GATGATTTTG

FIG. 7A

2521 AGGAGGCTAT TAGGGTATAT GCAAAGGTGG CACTTAGGCC AGATTGCAAG TACAAGATTA
2581 GCAAACTTGT AAATATCAGG AATTGTTGCT ACATTTCTGG GAACGGGGCC GAGGTGGAGA
2641 TAGATACGGA GGATAGGGTG GCCTTTAGAT GTAGCATGAT AAATATGTGG CCGGGGGTGC
2701 TTGGCATGGA CGGGGTGGTT ATTATGAATG TGAGGTTTAC TGGTCCCAAT TTTAGCGGTA
2761 CGGTTTTCCT GGCCAATACC AATCTTATCC TACACGGTGT AAGCTTCTAT GGGTTTAACA
2821 ATACCTGTGT GGAAGCCTGG ACCGATGTAA GGGTTCGGGG CTGTGCCTTT TACTGCTGCT
2881 GGAAGGGGGT GGTGTGTCGC CCCAAAAGCA GGGCTTCAAT TAAGAAATGC CTGTTTGAAA
2941 GGTGTACCTT GGGTATCCTG TCTGAGGGTA ACTCCAGGGT GCGCCACAAT GTGGCCTCCG
3001 ACTGTGGTTG CTTTATGCTA GTGAAAAGCG TGGCTGTGAT TAAGCATAAC ATGGTGTGTG
3061 GCAACTGCGA GGACAGGGCC TCTCAGATGC TGACCTGCTC GGACGGCAAC TGTCACTTGC
3121 TGAAGACCAT TCACGTAGCC AGCCACTCTC GCAAGGCCTG GCCAGTGTTT GAGCACAACA
3181 TACTGACCCG CTGTTCCTTG CATTTGGGTA ACAGGAGGGG GGTGTTCCTA CCTTACCAAT
3241 GCAATTTGAG TCACACTAAG ATATTGCTTG AGCCCGAGAG CATGTCCAAG GTGAACCTGA
3301 ACGGGGTGTT TGACATGACC ATGAAGATCT GGAAGGTGCT GAGGTACGAT GAGACCCGCA
3361 CCAGGTGCAG ACCCTGCGAG TGTGGCGGTA AACATATTAG GAACCAGCCT GTGATGCTGG
3421 ATGTGACCGA GGAGCTGAGG CCCGATCACT TGGTGCTGGC CTGCACCCGC GCTGAGTTTG
3481 GCTCTAGCGA TGAAGATACA GATTGAGGTA CTGAAATGTG TGGGCGTGGC TTAAGGGTGG
3541 GAAAGAATAT ATAAGGTGGG GGTCTCATGT AGTTTTGTAT CTGTTTTGCA GCAGCCGCCG
3601 CCATGAGCGC CAACTCGTTT GATGGAAGCA TTGTGAGCTC ATATTTGACA ACGCGCATGC
3661 CCCCATGGGC CGGGGTGCGT CAGAATGTGA TGGGCTCCAG CATTGATGGT CGCCCCGTCC
3721 TGCCCGCAAA CTCTACTACC TTGACCTACG AGACCGTGTC TGGAACGCCG TTGGAGACTG
3781 CAGCCTCCGC CGCCGCTTCA GCCGCTGCAG CCACCGCCCG CGGGATTGTG ACTGACTTTG
3841 CTTTCCTGAG CCCGCTTGCA AGCAGTGCAG CTTCCCGTTC ATCCGCCCGC GATGACAAGT
3901 TGACGGCTCT TTTGGCACAA TTGGATTCTT TGACCCGGGA ACTTAATGTC GTTTCTCAGC
3961 AGCTGTTGGA TCTGCGCCAG CAGGTTTCTG CCCTGAAGGC TTCCTCCCCT CCCAATGCGG
4021 TTTAAAACAT AAATAAAAAC CAGACTCTGT TTGGATTTGG ATCAAGCAAG TGTCTTGCTG
4081 TCTTTATTTA GGGGTTTTGC GCGCGCGGTA GGCCCGGGAC CAGCGGTCTC GGTCGTTGAG
4141 GGTCCTGTGT ATTTTTTCCA GGACGTGGTA AAGGTGACTC TGGATGTTCA GATACATGGG
4201 CATAAGCCCG TCTCTGGGGT GGAGGTAGCA CCACTGCAGA GCTTCATGCT GCGGGGTGGT
4261 GTTGTAGATG ATCCAGTCGT AGCAGGAGCG CTGGGCGTGG TGCCTAAAAA TGTCTTTCAG
4321 TAGCAAGCTG ATTGCCAGGG GCAGGCCCTT GGTGTAAGTG TTTACAAAGC GGTTAAGCTG
4381 GGATGGGTGC ATACGTGGGG ATATGAGATG CATCTTGGAC TGTATTTTTA GGTTGGCTAT
4441 GTTCCCAGCC ATATCCCTCC GGGGATTCAT GTTGTGCAGA ACCACCAGCA CAGTGTATCC
4501 GGTGCACTTG GGAAATTTGT CATGTAGCTT AGAAGGAAAT GCGTGGAAGA ACTTGGAGAC
4561 GCCCTTGTGA CCTCCAAGAT TTTCCATGCA TTCGTCCATA ATGATGGCAA TGGGCCCACG
4621 GGCGGCGGCC TGGGCGAAGA TATTTCTGGG ATCACTAACG TCATAGTTGT GTTCCAGGAT
4681 GAGATCGTCA TAGGCCATTT TTACAAAGCG CGGGCGGAGG GTGCCAGACT GCGGTATAAT
4741 GGTTCCATCC GGCCCAGGGG CGTAGTTACC CTCACAGATT TGCATTTCCC ACGCTTTGAG
4801 TTCAGATGGG GGGATCATGT CTACCTGCGG GGCGATGAAG AAAACCGTTT CCGGGGTAGG
4861 GGAGATCAGC TGGGAAGAAA GCAGGTTCCT AAGCAGCTGC GACTTACCGC AGCCGGTGGG
4921 CCCGTAAATC ACACCTATTA CCGGCTGCAA CTGGTAGTTA AGAGAGCTGC AGCTGCCGTC
4981 ATCCCTGAGC AGGGGGGCCA CTTCGTTAAG CATGTCCCTG ACTTGCATGT TTTCCCTGAC

FIG. 7B

5041 CAAATCCGCC AGAAGGCGCT CGCCGCCCAG CGATAGCAGT TCTTGCAAGG AAGCAAAGTT
5101 TTTCAACGGT TTGAGGCCGT CCGCCGTAGG CATGCTTTTG AGCGTTTGAC CAAGCAGTTC
5161 CAGGCGGTCC CACAGCTCGG TCACGTGCTC TACGGCATCT CGATCCAGCA TATCTCCTCG
5221 TTTCGCGGGT TGGGGCGGCT TTCGCTGTAC GGCAGTAGTC GGTGCTCGTC CAGACGGGCC
5281 AGGGTCATGT CTTTCCACGG GCGCAGGGTC CTCGTCAGCG TAGTCTGGGT CACGGTGAAG
5341 GGGTGCGCTC CGGGTTGCGC GCTGGCCAGG GTGCGCTTGA GGCTGGTCCT GCTGGTGCTG
5401 AAGCGCTGCC GGTCTTCGCC CTGCGCGTCG GCCAGGTAGC ATTTGACCAT GGTGTCATAG
5461 TCCAGCCCCT CCGCGGCGTG GCCCTTGGCG CGCAGCTTGC CCTTGGAGGA GGCGCCGCAC
5521 GAGGGGCAGT GCAGACTTTT AAGGGCGTAG AGCTTGGGCG CGAGAAATAC CGATTCCGGG
5581 GAGTAGGCAT CCGCGCCGCA GGCCCCGCAG ACGGTCTCGC ATTCCACGAG CCAGGTGAGC
5641 TCTGGCCGTT CGGGGTCAAA AACCAGGTTT CCCCCATGCT TTTTGATGCG TTTCTTACCT
5701 CTGGTTTCCA TGAGCCGGTG TCCACGCTCG GTGACGAAAA GGCTGTCCGT GTCCCCGTAT
5761 ACAGACTTGA GAGGCCTGTC CTCGAGCGGT GTTCCGCGGT CCTCCTCGTA TAGAAACTCG
5821 GACCACTCTG AGACGAAGGC TCGCGTCCAG GCCAGCACGA AGGAGGCTAA GTGGGAGGGG
5881 TAGCGGTCGT TGTCCACTAG GGGGTCCACT CGCTCCAGGG TGTGAAGACA CATGTCGCCC
5941 TCTTCGGCAT CAAGGAAGGT GATTGGTTTA TAGGTGTAGG CCACGTGACC GGGTGTTCCT
6001 GAAGGGGGGC TATAAAAGGG GGTGGGGGCG CGTTCGTCCT CACTCTCTTC CGCATCGCTG
6061 TCTGCGAGGG CCAGCTGTTG GGGTGAGTAC TCCCTCTCAA AAGCGGGCAT GACTTCTGCG
6121 CTAAGATTGT CAGTTTCCAA AAACGAGGAG GATTTGATAT TCACCTGGCC CGCGGTGATG
6181 CCTTTGAGGG TGGCCGCGTC CATCTGGTCA GAAAAGACAA TCTTTTTGTT GTCAAGCTTG
6241 GTGGCAAACG ACCCGTAGAG GGCGTTGGAC AGCAACTTGG CGATGGAGCG CAGGGTTTGG
6301 TTTTTGTCGC GATCGGCGCG CTCCTTGGCC GCGATGTTTA GCTGCACGTA TTCGCGCGCA
6361 ACGCACCGCC ATTCGGGAAA GACGGTGGTG CGCTCGTCGG GCACTAGGTG CACGCGCCAA
6421 CCGCGGTTGT GCAGGGTGAC AAGGTCAACG CTGGTGGCTA CCTCTCCGCG TAGGCGCTCG
6481 TTGGTCCAGC AGAGGCGGCC GCCCTTGCGC GAGCAGAATG GCGGTAGTGG GTCTAGCTGC
6541 GTCTCGTCCG GGGGGTCTGC GTCCACGGTA AAGACCCCGG GCAGCAGGCG CGCGTCGAAG
6601 TAGTCTATCT TGCATCCTTG CAAGTCTAGC GCCTGCTGCC ATGCGCGGGC GGCAAGCGCG
6661 CGCTCGTATG GGTTGAGTGG GGGACCCCAT GGCATGGGGT GGGTGAGCGC GGAGGCGTAC
6721 ATGCCGCAAA TGTCGTAAAC GTAGAGGGGC TCTCTGAGTA TTCCAAGATA TGTAGGGTAG
6781 CATCTTCCAC CGCGGATGCT GGCGCGCACG TAATCGTATA GTTCGTGCGA GGGAGCGAGG
6841 AGGTCGGGAC CGAGGTTGCT ACGGGCGGGC TGCTCTGCTC GGAAGACTAT CTGCCTGAAG
6901 ATGGCATGTG AGTTGGATGA TATGGTTGGA CGCTGGAAGA CGTTGAAGCT GGCGTCTGTG
6961 AGACCTACCG CGTCACGCAC GAAGGAGGCG TAGGAGTCGC GCAGCTTGTT GACCAGCTCG
7021 GCGGTGACCT GCACGTCTAG GGCGCAGTAG TCCAGGGTTT CCTTGATGAT GTCATACTTA
7081 TCCTGTCCCT TTTTTTTCCA CAGCTCGCGG TTGAGGACAA ACTCTTCGCG GTCTTTCCAG
7141 TACTCTTGGA TCGGAAACCC GTCGGCCTCC GAACGGTAAG AGCCTAGCAT GTAGAACTGG
7201 TTGACGGCCT GGTAGGCGCA GCATCCCTTT TCTACGGGTA GCGCGTATGC CTGCGCGGCC
7261 TTCCGGAGCG AGGTGTGGGT GAGCGCAAAG GTGTCCCTAA CCATGACTTT GAGGTACTGG
7321 TATTTGAAGT CAGTGTCGTC GCATCCGCCC TGCTCCCAGA GCAAAAAGTC CGTGCGCTTT
7381 TTGGAACGCG GGTTTGGCAG GGCGAAGGTG ACATCGTTGA AGAGTATCTT TCCCGCGCGA
7441 GGCATAAAGT TGCGTGTGAT GCGGAAGGGT CCCGGCACCT CGGAACGGTT GTTAATTACC
7501 TGGGCGGCGA GCACGATCTC GTCAAAGCCG TTGATGTTGT GGCCCACAAT GTAAAGTTCC

FIG. 7C

7561 AAGAAGCGCG GGATGCCCTT GATGGAAGGC AATTTTTTAA GTTCCTCGTA GGTGAGCTCT
7621 TCAGGGGAGC TGAGCCCGTG CTCTGAAAGG GCCCAGTCTG CAAGATGAGG GTTGGAAGCG
7681 ACGAATGAGC TCCACAGGTC ACGGGCCATT AGCATTTGCA GGTGGTCGCG AAAGGTCCTA
7741 AACTGGCGAC CTATGGCCAT TTTTTCTGGG GTGATGCAGT AGAAGGTAAG CGGGTCTTGT
7801 TCCCAGCGGT CCCATCCAAG GTCCGCGGCT AGGTCTCGCG CGGCGGTCAC TAGAGGCTCA
7861 TCTCCGCCGA ACTTCATGAC CAGCATGAAG GGCACGAGCT GCTTCCCAAA GGCCCCCATC
7921 CAAGTATAGG TCTCTACATC GTAGGTGACA AAGAGACGCT CGGTGCGAGG ATGCGAGCCG
7981 ATCGGGAAGA ACTGGATCTC CCGCCACCAG TTGGAGGAGT GGCTGTTGAT GTGGTGAAAG
8041 TAGAAGTCCC TGCGACGGGC CGAACACTCG TGCTGGCTTT TGTAAAAACG TGCGCAGTAC
8101 TGGCAGCGGT GCACGGGCTG TACATCCTGC ACGAGGTTGA CCTGACGACC GCGCACAAGG
8161 AAGCAGAGTG GGAATTTGAG CCCCTCGCCT GGCGGGTTTG GCTGGTGGTC TTCTACTTCG
8221 GCTGCTTGTC CTTGACCGTC TGGCTGCTCG AGGGGAGTTA CGGTGGATCG GACCACCACG
8281 CCGCGCGAGC CCAAAGTCCA GATGTCCGCG CGCGGCGGTC GGAGCTTGAT GACAACATCG
8341 CGCAGATGGG AGCTGTCCAT GGTCTGGAGC TCCCGCGGCG TCAGGTCAGG CGGGAGCTCC
8401 TGCAGGTTTA CCTCGCATAG CCGGGTCAGG GCGCGGGCTA GGTCCAGGTG ATACCTGATT
8461 TCCAGGGGCT GGTTGGTGGC GGCGTCGATG GCTTGCAAGA GGCCGCATCC CCGCGGCGCG
8521 ACTACGGTAC CGCGCGGCGG GCGGTGGGCC GCGGGGGTGT CCTTGGATGA TGCATCTAAA
8581 AGCGGTGACG CGGGCGGGCC CCCGGAGGTA GGGGGGGCTC GGGACCCGCC GGGAGAGGGG
8641 GCAGGGGCAC GTCGGCGCCG CGCGCGGGCA GGAGCTGGTG CTGCGCGCGG AGGTTGCTGG
8701 CGAACGCGAC GACGCGGCGG TTGATCTCCT GAATCTGGCG CCTCTGCGTG AAGACGACGG
8761 GCCCGGTGAG CTTGAACCTG AAAGAGAGTT CGACAGAATC AATTTCGGTG TCGTTGACGG
8821 CGGCCTGGCG CAAAATCTCC TGCACGTCTC CTGAGTTGTC TTGATAGGCG ATCTCGGCCA
8881 TGAACTGCTC GATCTCTTCC TCCTGGAGAT CTCCGCGTCC GGCTCGCTCC ACGGTGGCGG
8941 CGAGGTCGTT GGAGATGCGG GCCATGAGCT GCGAGAAGGC GTTGAGGCCT CCCTCGTTCC
9001 AGACGCGGCT GTAGACCACG CCCCCTTCGG CATCGCGGGC GCGCATGACC ACCTGCGCGA
9061 GATTGAGCTC CACGTGCCGG GCGAAGACGG CGTAGTTTCG CAGGCGCTGA AAGAGGTAGT
9121 TGAGGGTGGT GGCGGTGTGT TCTGCCACGA AGAAGTACAT AACCCAGCGC CGCAACGTGG
9181 ATTCGTTGAT ATCCCCCAAG GCCTCAAGGC GCTCCATGGC CTCGTAGAAG TCCACGGCGA
9241 AGTTGAAAAA CTGGGAGTTG CGCGCCGACA CGGTTAACTC CTCCTCCAGA AGACGGATGA
9301 GCTCGGCGAC AGTGTCGCGC ACCTCGCGCT CAAAGGCTAC AGGGGCCTCT TCTTCTTCTT
9361 CAATCTCCTC TTCCATAAGG GCCTCCCCTT CTTCTTCTTC TGGCGGCGGT GGGGGAGGGG
9421 GGACACGGCG GCGACGACGG CGCACCGGGA GGCGGTCGAC AAAGCGCTCG ATCATCTCCC
9481 CGCGGCGACG GCGCATGGTC TCGGTGACGG CGCGGCCGTT CTCGCGGGGG CGCAGTTGGA
9541 AGACGCCGCC CGTCATGTCC CGGTTATGGG TTGGCGGGGG GCTGCCGTGC GGCAGGGATA
9601 CGGCGCTAAC GATGCATCTC AACAATTGTT GTGTAGGTAC TCCGCCACCG AGGGACCTGA
9661 GCGAGTCCGC ATCGACCGGA TCGGAAAACC TCTCGAGAAA GGCGTCTAAC CAGTCACAGT
9721 CGCAAGGTAG GCTGAGCACC GTGGCGGGCG GCAGCGGGCG GCGGTCGGGG TTGTTTCTGG
9781 CGGAGGTGCT GCTGATGATG TAATTAAAGT AGGCGGTCTT GAGACGGCGG ATGGTCGACA
9841 GAAGCACCAT GTCCTTGGGT CCGGCCTGCT GAATGCGCAG GCGGTCGGCC ATGCCCCAGG
9901 CTTCGTTTTG ACATCGGCGC AGGTCTTTGT AGTAGTCTTG CATGAGCCTT TCTACCGGCA
9961 CTTCTTCTTC TCCTTCCTCT TGTCCTGCAT CTCTTGCATC TATCGCTGCG GCGGCGGCGG
10021 AGTTTGGCCG TAGGTGGCGC CCTCTTCCTC CCATGCGTGT GACCCCGAAG CCCCTCATCG

FIG. 7D

10081 GCTGAAGCAG GGCCAGGTCG GCGACAACGC GCTCGGCTAA TATGGCCTGC TGCACCTGCG
10141 TGAGGGTAGA CTGGAAGTCG TCCATGTCCA CAAAGCGGTG GTATGCGCCC GTGTTGATGG
10201 TGTAAGTGCA GTTGGCCATA ACGGACCAGT TAACGGTCTG GTGACCCGGC TGCGAGAGCT
10261 CGGTGTACCT GAGACGCGAG TAAGCCCTTG AGTCAAAGAC GTAGTCGTTG CAAGTCCGCA
10321 CCAGGTACTG GTATCCCACC AAAAAGTGCG GCGGCGGCTG GCGGTAGAGG GGCCAGCGTA
10381 GGGTGGCCGG GGCTCCGGGG GCGAGGTCTT CCAACATAAG GCGATGATAT CCGTAGATGT
10441 ACCTGGACAT CCAGGTGATG CCGGCGGCGG TGGTGGAGGC GCGCGGAAAG TCACGGACGC
10501 GGTTCCAGAT GTTGCGCAGC GGCAAAAAGT GCTCCATGGT CGGGACGCTC TGGCCGGTCA
10561 GGCGCGCGCA GTCGTTGACG CTCTAGACCG TGCAAAAGGA GAGCCTGTAA GCGGGCACTC
10621 TTCCGTGGTC TGGTGGATAA ATTCGCAAGG GTATCATGGC GGACGACCGG GGTTCGAACC
10681 CCGGATCCGG CCGTCCGCCG TGATCCATGC GGTTACCGCC CGCGTGTCGA ACCCAGGTGT
10741 GCGACGTCAG ACAACGGGGG AGCGCTCCTT TTGGCTTCCT TCCAGGCGCG GCGGATGCTG
10801 CGCTAGCTTT TTTGGCCACT GGCCGCGCGC GGCGTAAGCG GTTAGGCTGG AAAGCGAAAG
10861 CATTAAGTGG CTCGCTCCCT GTAGCCGGAG GGTTATTTTC CAAGGGTTGA GTCGCGGGAC
10921 CCCCGGTTCG AGTCTCGGGC CGGCCGGACT GCGGCGAACG GGGGTTTGCC TCCCCGTCAT
10981 GCAAGACCCC GCTTGCAAAT TCCTCCGGAA ACAGGGACGA GCCCCTTTTT TGCTTTTCCC
11041 AGATGCATCC GGTGCTGCGG CAGATGCGCC CCCCTCCTCA GCAGCGGCAA GAGCAAGAGC
11101 AGCGGCAGAC ATGCAGGGCA CCCTCCCCTT CTCCTACCGC GTCAGGAGGG GCAACATCCG
11161 CGGCTGACGC GGCGGCAGAT GGTGATTACG AACCCCCGCG GCGCCGGACC CGGCACTACT
11221 TGGACTTGGA GGAGGGCGAG GGCCTGGCGC GGCTAGGAGC GCCCTCTCCT GAGCGACACC
11281 CAAGGGTGCA GCTGAAGCGT GACACGCGCG AGGCGTACGT GCCGCGGCAG AACCTGTTTC
11341 GCGACCGCGA GGGAGAGGAG CCCGAGGAGA TGCGGGATCG AAAGTTCCAT GCAGGGCGCG
11401 AGTTGCGGCA TGGCCTGAAC CGCGAGCGGT TGCTGCGCGA GGAGGACTTT GAGCCCGACG
11461 CGCGGACCGG GATTAGTCCC GCGCGCGCAC ACGTGGCGGC CGCCGACCTG GTAACCGCGT
11521 ACGAGCAGAC GGTGAACCAG GAGATTAACT TTCAAAAAAG CTTTAACAAC CACGTGCGCA
11581 CGCTTGTGGC GCGCGAGGAG GTGGCTATAG GACTGATGCA TCTGTGGGAC TTTGTAAGCG
11641 CGCTGGAGCA AAACCCAAAT AGCAAGCCGC TCATGGCGCA GCTGTTCCTT ATAGTGCAGC
11701 ACAGCAGGGA CAACGAGGCA TTCAGGGATG CGCTGCTAAA CATAGTAGAG CCCGAGGGCC
11761 GCTGGCTGCT CGATTTGATA AACATTCTGC AGAGCATAGT GGTGCAGGAG CGCAGCTTGA
11821 GCCTGGCTGA CAAGGTGGCC GCCATTAACT ATTCCATGCT CAGTCTGGGC AAGTTTTACG
11881 CCCGCAAGAT ATACCATACC CCTTACGTTC CCATAGACAA GGAGGTAAAG ATCGAGGGGT
11941 TCTACATGCG CATGGCGCTG AAGGTGCTTA CCTTGAGCGA CGACCTGGGC GTTTATCGCA
12001 ACGAGCGCAT CCACAAGGCC GTGAGCGTGA GCCGGCGGCG CGAGCTCAGC GACCGCGAGC
12061 TGATGCACAG CCTGCAAAGG GCCCTGGCTG GCACGGGCAG CGGCGATAGA GAGGCCGAGT
12121 CCTACTTTGA CGCGGGCGCT GACCTGCGCT GGGCCCCAAG CCGACGCGCC CTGGAGGCAG
12181 CTGGGGCCGG ACCTGGGCTG GCGGTGGCAC CCGCGCGCGC TGGCAACGTC GGCGGCGTGG
12241 AGGAATATGA CGAGGACGAT GAGTACGAGC CAGAGGACGG CGAGTACTAA GCGGTGATGT
12301 TTCTGATCAG ATGATGCAAG ACGCAACGGA CCCGGCGGTG CGGGCGGCGC TGCAGAGCCA
12361 GCCGTCCGGC CTTAACTCCA CGGACGACTG GCGCCAGGTC ATGGACCGCA TCATGTCGCT
12421 GACTGCGCGC AACCCTGACG CGTTCCGGCA GCAGCCGCAG GCCAACCGGC TCTCCGCAAT
12481 TCTGGAAGCG GTGGTCCCGG CGCGCGCAAA CCCCACGCAC GAGAAGGTGC TGGCGATCGT
12541 AAACGCGCTG GCCGAAAACA GGGCCATCCG GCCCGATGAG GCCGGCCTGG TCTACGACGC

FIG. 7E

12601 GCTGCTTCAG CGCGTGGCTC GTTACAACAG CAGCAACGTG CAGACCAACC TGGACCGGCT
12661 GGTGGGGGAT GTGCGCGAGG CCGTGGCGCA GCGTGAGCGC GCGCAGCAGC AGGGCAACCT
12721 GGGCTCCATG GTTGCACTAA ACGCCTTCCT GAGTACACAG CCCGCCAACG TGCCGCGGGG
12781 ACAGGAGGAC TACACCAACT TTGTGAGCGC ACTGCGGCTA ATGGTGACTG AGACACCGCA
12841 AAGTGAGGTG TATCAGTCCG GGCCAGACTA TTTTTTCCAG ACCAGTAGAC AAGGCCTGCA
12901 GACCGTAAAC CTGAGCCAGG CTTTCAAGAA CTTGCAGGGG CTGTGGGGGG TGCGGGCTCC
12961 CACAGGCGAC CGCGCGACCG TGTCTAGCTT GCTGACGCCC AACTCGCGCC TGTTGCTGCT
13021 GCTAATAGCG CCCTTCACGG ACAGTGGCAG CGTGTCCCGG GACACATACC TAGGTCACTT
13081 GCTGACACTG TACCGCGAGG CCATAGGTCA GGCGCATGTG GACGAGCATA CTTTCCAGGA
13141 GATTACAAGT GTTAGCCGCG CGCTGGGGCA GGAGGACACG GGCAGCCTGG AGGCAACCCT
13201 GAACTACCTG CTGACCAACC GGCGGCAAAA AATCCCCTCG TTGCACAGTT TAAACAGCGA
13261 GGAGGAGCGC ATTTTGCGCT ATGTGCAGCA GAGCGTGAGC CTTAACCTGA TGCGCGACGG
13321 GGTAACGCCC AGCGTGGCGC TGGACATGAC CGCGCGCAAC ATGGAACCGG GCATGTATGC
13381 CTCAAACCGG CCGTTTATCA ATCGCCTAAT GGACTACTTG CATCGCGCGG CCGCCGTGAA
13441 CCCCGAGTAT TTCACCAATG CCATCTTGAA CCCGCACTGG CTACCGCCCC CTGGTTTCTA
13501 CACCGGGGGA TTCGAGGTGC CCGAGGGTAA CGATGGATTC CTCTGGGACG ACATAGACGA
13561 CAGCGTGTTT TCCCCGCAAC CGCAGACCCT GCTAGAGTTG CAACAACGCG AGCAGGCAGA
13621 GGCGGCGCTG CGAAAGGAAA GCTTCCGCAG GCCAAGCAGC TTGTCCGATC TAGGCGCTGC
13681 GGCCCCGCGG TCAGATGCTA GTAGCCCATT TCCAAGCTTG ATAGGGTCTC TTACCAGCAC
13741 TCGCACCACC CGCCCGCGCC TGCTGGGCGA GGAGGAGTAC CTAAACAACT CGCTGCTGCA
13801 GCCGCAGCGC GAAAAGAACC TGCCTCCGGC GTTTCCCAAC AACGGGATAG AGAGCCTAGT
13861 GGACAAGATG AGTAGATGGA AGACGTATGC GCAGGAGCAC AGGGATGTGC CCGGCCCGCG
13921 CCCGCCCACC CGTCGTCAAA GGCACGACCG TCAGCGGGGT CTGGTGTGGG AGGACGATGA
13981 CTCGGCAGAC GACAGCAGCG TCTTGGATTT GGGAGGGAGT GGCAACCCGT TTGCACACCT
14041 TCGCCCCAGG CTGGGGAGAA TGTTTTAAAA AAAGCATGAT GCAAAATAAA AAACTCACCA
14101 AGGCCATGGC ACCGAGCGTT GGTTTTCTTG TATTCCCCTT AGTATGCGGC GCGCGGCGAT
14161 GTATGAGGAA GGTCCTCCTC CCTCCTACGA GAGCGTGGTG AGCGCGGCGC CAGTGGCGGC
14221 GGCGCTGGGT TCACCCTTCG ATGCTCCCCT GGACCCGCCG TTCGTGCCTC CGCGGTACCT
14281 GCGGCCTACC GGGGGGAGAA ACAGCATCCG TTACTCTGAG TTGGCACCCC TATTCGACAC
14341 CACCCGTGTG TACCTTGTGG ACAACAAGTC AACGGATGTG GCATCCCTGA ACTACCAGAA
14401 CGACCACAGC AACTTTCTAA CCACGGTCAT TCAAAACAAT GACTACAGCC CGGGGGAGGC
14461 AAGCACACAG ACCATCAATC TTGACGACCG GTCGCACTGG GGCGGCGACC TGAAAACCAT
14521 CCTGCATACC AACATGCCAA ATGTGAACGA GTTCATGTTT ACCAATAAGT TTAAGGCGCG
14581 GGTGATGGTG TCGCGCTCGC TTACTAAGGA CAAACAGGTG GAGCTGAAAT ACGAGTGGGT
14641 GGAGTTCACG CTGCCCGAGG GCAACTACTC CGAGACCATG ACCATAGACC TTATGAACAA
14701 CGCGATCGTG GAGCACTACT TGAAAGTGGG CAGGCAGAAC GGGGTTCTGG AAAGCGACAT
14761 CGGGGTAAAG TTTGACACCC GCAACTTCAG ACTGGGGTTT GACCCAGTCA CTGGTCTTGT
14821 CATGCCTGGG GTATATACAA ACGAAGCCTT CCATCCAGAC ATCATTTTGC TGCCAGGATG
14881 CGGGGTGGAC TTCACCCACA GCCGCCTGAG CAACTTGTTG GGCATCCGCA AGCGGCAACC
14941 CTTCCAGGAG GGCTTTAGGA TCACCTACGA TGACCTGGAG GGTGGTAACA TTCCCGCACT
15001 GTTGGATGTG GACGCCTACC AGGCAAGCTT GAAAGATGAC ACCGAACAGG GCGGGGGTGG
15061 CGCAGGCGGC GGCAACAACA GTGGCAGCGG CGCGGAAGAG AACTCCAACG CGGCAGCTGC

FIG. 7F

15121 GGCAATGCAG CCGGTGGAGG ACATGAACGA TCATGCCATT CGCGGCGACA CCTTTGCCAC
15181 ACGGGCGGAG GAGAAGCGCG CTGAGGCCGA GGCAGCGGCC GAAGCTGCCG CCCCCGCTGC
15241 GGAGGCTGCA CAACCCGAGG TCGAGAAGCC TCAGAAGAAA CCGGTGATTA AACCCCTGAC
15301 AGAGGACAGC AAGAAACGCA GTTACAACCT AATAAGCAAT GACAGCACCT TCACCCAGTA
15361 CCGCAGCTGG TACCTTGCAT ACAACTACGG CGACCCTCAG GCCGGGATCC GCTCATGGAC
15421 CCTGCTTTGC ACTCCTGACG TAACCTGCGG CTCGGAGCAG GTATACTGGT CGTTGCCCGA
15481 CATGATGCAA GACCCCGTGA CCTTCCGCTC CACGCGCCAG ATCAGCAACT TTCCGGTGGT
15541 GGGCGCCGAG CTGTTGCCCG TGCACTCCAA GAGCTTCTAC AACGACCAGG CCGTCTACTC
15601 CCAGCTCATC CGCCAGTTTA CCTCTCTGAC CCACGTGTTC AATCGCTTTC CCGAGAACCA
15661 GATTTTGGCG CGCCCGCCAG CCCCCACCAT CACCACCGTC AGTGAAAACG TTCCTGCTCT
15721 CACAGATCAC GGGACGCTAC CGCTGCGCAA CAGCATCGGA GGAGTCCAGC GAGTGACCAT
15781 TACTGACGCC AGACGCCGCA CCTGCCCCTA CGTTTACAAG GCCCTGGGCA TAGTCTCGCC
15841 GCGCGTCCTA TCGAGCCGCA CTTTTTGAGC AAGCATGTCC ATCCTTATAT CGCCCAGCAA
15901 TAACACAGGC TGGGGCCTGC GCTTCCCAAG CAAGATGTTT GGCGGGGCCA AGAAGCGCTC
15961 CGACCAACAC CCAGTGCGCG TGCGCGGGCA CTACCGCGCG CCCTGGGGCG CGCACAAACG
16021 CGGCCGCACT GGGCGCACCA CCGTCGATGA CGCCATCGAC GCGGTGGTGG AGGAGGCGCG
16081 CAACTACACG CCCACGCCGC CGCCAGTGTC CACCGTGGAC GCGGCCATTC AGACCGTGGT
16141 GCGCGGAGCC CGGCGCTACG CTAAAATGAA GAGACGGCGG AGGCGCGTAG CACGTCGCCA
16201 CCGCCGCCGA CCCGGCACTG CCGCCCAACG CGCGGCGGCG GCCCTGCTTA ACCGCGCACG
16261 TCGCACCGGC CGACGGGCGG CCATGCGAGC CGCTCGAAGG CTGGCCGCGG GTATTGTCAC
16321 TGTGCCCCCC AGGTCCAGGC GACGAGCGGC CGCCGCAGCA GCCGCGGCCA TTAGTGCTAT
16381 GACTCAGGGT CGCAGGGGCA ACGTGTACTG GGTGCGCGAC TCGGTTAGCG GCCTGCGCGT
16441 GCCCGTGCGC ACCCGCCCCC CGCGCAACTA GATTGCAATA AAAAACTACT TAGACTCGTA
16501 CTGTTGTATG TATCCAGCGG CGGCGGCGCG CATCGAAGCT ATGTCCAAGC GCAAAATCAA
16561 AGAAGAGATG CTCCAGGTCA TCGCGCCGGA GATCTATGGC CCCCCGAAGA AGGAAGAGCA
16621 GGATTACAAG CCCCGAAAGC TAAAGCGGGT CAAAAAGAAA AAGAAAGATG ATGATGATGA
16681 TGAACTTGAC GACGAGGTGG AACTGTTGCA CGCGACCGCG CCCAGGCGAC GGGTACAGTG
16741 GAAAGGTCGA CGCGTAAGAC GTGTTTTGCG ACCCGGCACC ACCGTAGTCT TTACGCCCGG
16801 TGAGCGCTCC ACCCGCACCT ACAAGCGCGT GTATGATGAG GTGTACGGCG ACGAGGACCT
16861 GCTTGAGCAG GCCAACGAGC GCCTCGGGGA GTTTGCCTAC GGAAAGCGGC ATAAGGACAT
16921 GCTGGCGTTG CCGCTGGACG AGGGCAACCC AACACCTAGC CTAAAGCCCG TGACACTGCA
16981 GCAGGTGCTG CCCGCGCTTG CACCGTCCGA AGAAAAGCGC GGCCTAAAGC GCGAGTCTGG
17041 TGACTTGGCA CCCACCGTGC AGCTGATGGT ACCCAAGCGT CAGCGACTGG AAGATGTCTT
17101 GGAAAAAATG ACCGTGGAGC CTGGGCTGGA GCCCGAGGTC CGCGTGCGGC CAATCAAGCA
17161 GGTGGCACCG GGACTGGGCG TGCAGACCGT GGACGTTCAG ATACCCACCA CCAGTAGCAC
17221 TAGTATTGCC ACTGCCACAG AGGGCATGGA GACACAAACG TCCCCGGTTG CCTCGGCGGT
17281 GGCAGATGCC GCGGTGCAGG CGGCCGCTGC GGCCGCGTCC AAGACCTCTA CGGAGGTGCA
17341 AACGGACCCG TGGATGTTTC GTGTTTCAGC CCCCCGGCGT CCGCGCCGTT CAAGGAAGTA
17401 CGGCGCCGCC AGCGCGCTAC TGCCCGAATA TGCCCTACAT CCTTCCATCG CGCCTACCCC
17461 CGGCTATCGT GGCTACACCT ACCGCCCCAG AAGACGAGCA ACTACCCGAC GCCGAACCAC
17521 CACTGGAACC CGCCGCCGCC GTCGCCGTCG CCAGCCCGTG CTGGCCCCGA TTTCCGTGCG
17581 CAGGGTGGCT CGCGAAGGAG GCAGGACCCT GGTGCTGCCA ACAGCGCGCT ACCACCCCAG

FIG. 7G

17641 CATCGTTTAA AAGCCGGTCT TTGTGGTTCT TGCAGATATG GCCCTCACCT GCCGCCTCCG
17701 TTTCCCGGTG CCGGGATTCC GAGGAAGAAT GCACCGTAGG AGGGGCATGG CCGGCCACGG
17761 CCTGACGGGC GGCATGCGTC GTGCGCACCA CCGGCGGCGG CGCGCGTCGC ACCGTCGCAT
17821 GCGCGGCGGT ATCCTGCCCC TCCTTATTCC ACTGATCGCC GCGGCGATTG GCGCCGTGCC
17881 CGGAATTGCA TCCGTGGCCT TGCAGGCGCA GAGACACTGA TTAAAAACAA GTTACATGTG
17941 GAAAAATCAA AATAAAAGTC TGGACTCTCA CGCTCGCTTG GTCCTGTAAC TATTTTGTAG
18001 AATGGAAGAC ATCAACTTTG CGTCACTGGC CCCGCGACAC GGCTCGCGCC CGTTCATGGG
18061 AAACTGGCAA GATATCGGCA CCAGCAATAT GAGCGGTGGC GCCTTCAGCT GGGGCTCGCT
18121 GTGGAGCGGC ATTAAAAATT TCGGTTCCGC CGTTAAGAAC TATGGCAGCA AAGCCTGGAA
18181 CAGCAGCACA GGCCAGATGC TGAGGGACAA GTTGAAAGAG CAAAATTTCC AACAAAAGGT
18241 GGTAGATGGC CTGGCCTCTG GCATTAGCGG GGTGGTGGAC CTGGCCAACC AGGCAGTGCA
18301 AAATAAGATT AACAGTAAGC TTGATCCCCG CCCTCCCGTA GAGGAGCCTC CACCGGCCGT
18361 GGAGACAGTG TCTCCAGAGG GGCGTGGCGA AAAGCGTCCG CGACCCGACA GGGAAGAAAC
18421 TCTGGTGACG CAAATAGACG AGCCTCCCTC GTACGAGGAG GCACTAAAGC AAGGCCTGCC
18481 CACCACCCGT CCCATCGCGC CCATGGCTAC CGGAGTGCTG GGCCAGCACA CACCCGTAAC
18541 GCTGGACCTG CCTCCCCCCG CCGACACCCA GCAGAAACCT GTGCTGCCAG GCCCGTCCGC
18601 CGTTGTTGTA ACCCGTCCTA GCCGCGCGTC CCTGCGCCGC GCCGCCAGCG GTCCGCGATC
18661 GTTGCGGCCC GTAGCCAGTG GCAACTGGCA AAGCACACTG AACAGCATCG TGGGTTTGGG
18721 GGTGCAATCC CTGAAGCGCC GACGATGCTT CTGATAGCTA ACGTGTCGTA TGTGTGTCAT
18781 GTATGCGTCC ATGTCGCCGC CAGAGGAGCT GCTGAGCCGC CGCGCGCCCG CTTTCCAAGA
18841 TGGCTACCCC TTCGATGATG CCGCAGTGGT CTTACATGCA CATCTCGGGC CAGGACGCCT
18901 CGGAGTACCT GAGCCCCGGG CTGGTGCAGT TCGCCCGCGC CACCGAGACG TACTTCAGCC
18961 TGAATAACAA GTTTAGAAAC CCCACGGTGG CGCCTACGCA CGACGTGACC ACAGACCGGT
19021 CTCAGCGTTT GACGCTGCGG TTCATCCCCG TGGACCGCGA GGATACTGCG TACTCGTACA
19081 AGGCGCGGTT CACCCTAGCT GTGGGTGATA ACCGTGTGCT AGACATGGCT TCCACGTACT
19141 TTGACATCCG CGGCGTGCTG GACAGGGGCC CTACTTTTAA GCCCTACTCT GGCACTGCCT
19201 ACAACGCACT GGCCCCCAAG GGTGCCCCCA ACTCGTGCGA GTGGGAACAA AATGAAACTG
19261 CACAAGTGGA TGCTCAAGAA CTTGACGAAG AGGAGAATGA AGCCAATGAA GCTCAGGCGC
19321 GAGAACAGGA ACAAGCTAAG AAAACCCATG TATATGCCCA GGCTCCACTG TCCGGAATAA
19381 AAATAACTAA AGAAGGTCTA CAAATAGGAA CTGCCGACGC CACAGTAGCA GGTGCCGGCA
19441 AAGAAATTTT CGCAGACAAA ACTTTTCAAC CTGAACCACA AGTAGGAGAA TCTCAATGGA
19501 ACGAAGCGGA TGCCACAGCA GCTGGTGGAA GGGTTCTTAA AAAGACAACT CCCATGAAAC
19561 CCTGCTATGG CTCATACGCT AGACCCACCA ATTCCAACGG CGGACAGGGC GTTATGGTTG
19621 AACAAAATGG TAAATTGGAA AGTCAAGTCG AAATGCAATT TTTTTCCACA TCCACAAATG
19681 CCACAAATGA AGTTAACAAT ATACAACCAA CAGTTGTATT GTACAGCGAA GATGTAAACA
19741 TGGAAACTCC AGATACTCAT CTTTCTTATA AACCTAAAAT GGGGGATAAA AATGCCAAAG
19801 TCATGCTTGG ACAACAAGCA ATGCCAAACA GACCAAATTA CATTGCTTTT AGAGACAATT
19861 TTATTGGTCT CATGTATTAC AACAGCACAG GTAACATGGG TGTCCTTGCT GGTCAGGCAT
19921 CGCAGTTGAA CGCTGTTGTA GATTTGCAAG ACAGAAACAC AGAGCTGTCC TACCAGCTTT
19981 TGCTTGATTC AATTGGCGAC AGAACAAGAT ACTTTTCAAT GTGGAATCAA GCTGTTGACA
20041 GCTATGATCC AGATGTCAGA ATTATTGAGA ACCATGGAAC TGAGGATGAG TTGCCAAATT
20101 ATTGCTTTCC TCTTGGTGGA ATTGGGATTA CTGACACTTT TCAAGCTGTT AAAACAACTG

FIG. 7H

20161 CTGCTAACGG GGACCAAGGC AATACTACCT GGCAAAAAGA TTCAACATTT GCAGAACGCA
20221 ATGAAATAGG GGTGGGAAAT AACTTTGCCA TGGAAATTAA CCTGAATGCC AACCTATGGA
20281 GAAATTTCCT TTACTCCAAT ATTGCGCTGT ACCTGCCAGA CAAGCTAAAA TACAACCCCA
20341 CCAATGTGGA AATATCTGAC AACCCCAACA CCTACGACTA CATGAACAAG CGAGTGGTGG
20401 CTCCTGGGCT TGTAGACTGC TACATTAACC TTGGGGCGCG CTGGTCTCTG GACTACATGG
20461 ACAACGTTAA TCCCTTTAAC CACCACCGCA ATGCGGGCCT GCGTTACCGC TCCATGTTGT
20521 TGGGAAACGG CCGCTACGTG CCCTTTCACA TTCAGGTGCC CCAAAAGTTT TTTGCCATTA
20581 AAAACCTCCT CCTCCTGCCA GGCTCATACA CATATGAATG GAACTTCAGG AAGGATGTTA
20641 ACATGGTTCT GCAGAGCTCT CTGGGAAACG ACCTTAGAGT TGACGGGGCT AGCATTAAGT
20701 TTGACAGCAT TTGTCTTTAC GCCACCTTCT TCCCCATGGC CCACAACACG GCCTCCACGC
20761 TGGAAGCCAT GCTCAGAAAT GACACCAACG ACCAGTCCTT TAATGACTAC CTTTCCGCCG
20821 CCAACATGCT ATATCCCATA CCCGCCAACG CCACCAACGT GCCCATCTCC ATCCCATCGC
20881 GCAACTGGGC AGCATTTCGC GGTTGGGCCT TCACACGCTT GAAGACAAAG GAAACCCCTT
20941 CCCTGGGATC AGGCTACGAC CCTTACTACA CCTACTCTGG CTCCATACCA TACCTTGACG
21001 GAACCTTCTA TCTTAATCAC ACCTTTAAGA AGGTGGCCAT TACTTTTGAC TCTTCTGTTA
21061 GCTGGCCGGG CAACGACCGC CTGCTTACTC CCAATGAGTT TGAGATTAAG CGCTCAGTTG
21121 ACGGGGAGGG CTATAACGTA GCTCAGTGCA ACATGACAAA GGACTGGTTC CTAGTGCAGA
21181 TGTTGGCCAA CTACAATATT GGCTACCAGG GCTTCTACAT TCCAGAAAGC TACAAAGACC
21241 GCATGTACTC GTTCTTCAGA AACTTCCAGC CCATGAGCCG GCAAGTGGTG GACGATACTA
21301 AATACAAAGA TTATCAGCAG GTTGGAATTA TCCACCAGCA TAACAACTCA GGCTTCGTAG
21361 GCTACCTCGC TCCCACCATG CGCGAGGGAC AAGCTTACCC CGCTAATGTT CCCTACCCAC
21421 TAATAGGCAA AACCGCGGTT GATAGTATTA CCCAGAAAAA GTTTCTTTGC GACCGCACCC
21481 TGTGGCGCAT CCCCTTCTCC AGTAACTTTA TGTCCATGGG TGCGCTCACA GACCTGGGCC
21541 AAAACCTTCT CTACGCAAAC TCCGCCCACG CGCTAGACAT GACCTTTGAG GTGGATCCCA
21601 TGGACGAGCC CACCCTTCTT TATGTTTTGT TTGAAGTCTT TGACGTGGTC CGTGTGCACC
21661 AGCCGCACCG CGGCGTCATC GAGACCGTGT ACCTGCGCAC GCCCTTCTCG GCCGGCAACG
21721 CCACAACATA AAGAAGCAAG CAACATCAAC AACAGCTGCC GCCATGGGCT CCAGTGAGCA
21781 GGAACTGAAA GCCATTGTCA AAGATCTTGG TTGTGGGCCA TATTTTTTGG GCACCTATGA
21841 CAAGCGCTTC CCAGGCTTTG TTTCCCCACA CAAGCTCGCC TGCGCCATAG TTAACACGGC
21901 CGGTCGCGAG ACTGGGGGCG TACACTGGAT GGCCTTTGCC TGGAACCCGC GCTCAAAAAC
21961 ATGCTACCTC TTTGAGCCCT TTGGCTTTTC TGACCAACGT CTCAAGCAGG TTTACCAGTT
22021 TGAGTACGAG TCACTCCTGC GCCGTAGCGC CATTGCCTCT TCCCCCGACC GCTGTATAAC
22081 GCTGGAAAAG TCCACCCAAA GCGTGCAGGG GCCCAACTCG GCCGCCTGTG GCCTATTCTG
22141 CTGCATGTTT CTCCACGCCT TTGCCAACTG GCCCCAAACT CCCATGGATC ACAACCCCAC
22201 CATGAACCTT ATTACCGGGG TACCCAACTC CATGCTTAAC AGTCCCCAGG TACAGCCCAC
22261 CCTGCGCCGC AACCAGGAAC AGCTCTACAG CTTCCTGGAG CGCCACTCGC CCTACTTCCG
22321 CAGCCACAGT GCGCAAATTA GGAGCGCCAC TTCTTTTTGT CACTTGAAAA ACATGTAAAA
22381 ATAATGTACT AGGAGACACT TTCAATAAAG GCAAATGTTT TTATTTGTAC ACTCTCGGGT
22441 GATTATTTAC CCCCACCCTT GCCGTCTGCG CCGTTTAAAA ATCAAAGGGG TTCTGCCGCG
22501 CATCGCTATG CGCCACTGGC AGGGACACGT TGCGATACTG GTGTTTAGTG CTCCACTTAA
22561 ACTCAGGCAC AACCATCCGC GGCAGCTCGG TGAAGTTTTC ACTCCACAGG CTGCGCACCA
22621 TCACCAACGC GTTTAGCAGG TCGGGCGCCG ATATCTTGAA GTCGCAGTTG GGGCCTCCGC

FIG. 7I

22681 CCTGCGCGCG CGAGTTGCGA TACACAGGGT TACAGCACTG GAACACTATC AGCGCCGGGT
22741 GGTGCACGCT GGCCAGCACG CTCTTGTCGG AGATCAGATC CGCGTCCAGG TCCTCCGCGT
22801 TGCTCAGGGC GAACGGAGTC AACTTTGGTA GCTGCCTTCC CAAAAAGGGT GCATGCCCAG
22861 GCTTTGAGTT GCACTCGCAC CGTAGTGGCA TCAGAAGGTG ACCGTGCCCA GTCTGGGCGT
22921 TAGGATACAG CGCCTGCATG AAAGCCTTGA TCTGCTTAAA AGCCACCTGA GCCTTTGCGC
22981 CTTCAGAGAA GAACATGCCG CAAGACTTGC CGGAAAACTG ATTGGCCGGA CAGGCCGCGT
23041 CATGCACGCA GCACCTTGCG TCGGTGTTGG AGATCTGCAC CACATTTCGG CCCCACCGGT
23101 TCTTCACGAT CTTGGCCTTG CTAGACTGCT CCTTCAGCGC GCGCTGCCCG TTTTCGCTCG
23161 TCACATCCAT TTCAATCACG TGCTCCTTAT TTATCATAAT GCTCCCGTGT AGACACTTAA
23221 GCTCGCCTTC GATCTCAGCG CAGCGGTGCA GCCACAACGC GCAGCCCGTG GGCTCGTGGT
23281 GCTTGTAGGT TACCTCTGCA AACGACTGCA GGTACGCCTG CAGGAATCGC CCCATCATCG
23341 TCACAAAGGT CTTGTTGCTG GTGAAGGTCA GCTGCAACCC GCGGTGCTCC TCGTTTAGCC
23401 AGGTCTTGCA TACGGCCGCC AGAGCTTCCA CTTGGTCAGG CAGTAGCTTG AAGTTTGCCT
23461 TTAGATCGTT ATCCACGTGG TACTTGTCCA TCAACGCGCG CGCAGCCTCC ATGCCCTTCT
23521 CCCACGCAGA CACGATCGGC AGGCTCAGCG GGTTTATCAC CGTGCTTTCA CTTTCCGCTT
23581 CACTGGACTC TTCCTTTTCC TCTTGCATCC GCATACCCCG CGCCACTGGG TCGTCTTCAT
23641 TCAGCCGCCG CACCGTGCGC TTACCTCCCT TGCCGTGCTT GATTAGCACC GGTGGGTTGC
23701 TGAAACCCAC CATTTGTAGC GCCACATCTT CTCTTTCTTC CTCGCTGTCC ACGATCACCT
23761 CTGGGGATGG CGGGCGCTCG GGCTTGGGAG AGGGGCGCTT CTTTTTCTTT TTGGACGCAA
23821 TGGCCAAATC CGCCGTCGAG GTCGATGGCC GCGGGCTGGG TGTGCGCGGC ACCAGCGCAT
23881 CTTGTGACGA GTCTTCTTCG TCCTCGGACT CGAGACGCCG CCTCAGCCGC TTTTTTGGGG
23941 GCGCGCGGGG AGGCGGCGGC GACGGCGACG GGGACGAGAC GTCCTCCATG GTTGGTGGAC
24001 GTCGCGCCGC ACCGCGTCCG CGCTCGGGGG TGGTTTCGCG CTGCTCCTCT TCCCGACTGG
24061 CCATTTCCTT CTCCTATAGG CAGAAAAAGA TCATGGAGTC AGTCGAGAAG GAGGACAGCC
24121 TAACCGCCCC CTTTGAGTTC GCCACCACCG CCTCCACCGA TGCCGCCAAC GCGCCTACCA
24181 CCTTCCCCGT CGAGGCACCC CCGCTTGAGG AGGAGGAAGT GATTATCGAG CAGGACCCAG
24241 GTTTTGTAAG CGAAGACGAC GAAGATCGCT CAGTACCAAC AGAGGATAAA AAGCAAGACC
24301 AGGACGACGC AGAGGCAAAC GAGGAACAAG TCGGGCGGGG GGACCAAAGG CATGGCGACT
24361 ACCTAGATGT GGGAGACGAC GTGCTGTTGA AGCATCTGCA GCGCCAGTGC GCCATTATCT
24421 GCGACGCGTT GCAAGAGCGC AGCGATGTGC CCCTCGCCAT AGCGGATGTC AGCCTTGCCT
24481 ACGAACGCCA CCTGTTCTCA CCGCGCGTAC CCCCCAAACG CCAAGAAAAC GGCACATGCG
24541 AGCCCAACCC GCGCCTCAAC TTCTACCCCG TATTTGCCGT GCCAGAGGTG CTTGCCACCT
24601 ATCACATCTT TTTCCAAAAC TGCAAGATAC CCCTATCCTG CCGTGCCAAC CGCAGCCGAG
24661 CGGACAAGCA GCTGGCCTTG CGGCAGGGCG CTGTCATACC TGATATCGCC TCGCTCGACG
24721 AAGTGCCAAA AATCTTTGAG GGTCTTGGAC GCGACGAGAA GCGCGCGGCA AACGCTCTGC
24781 AACAAGAAAA CAGCGAAAAT GAAAGTCACT GTGGAGTGCT GGTGGAACTT GAGGGTGACA
24841 ACGCGCGCCT AGCCGTGCTG AAACGCAGCA TCGAGGTCAC CCACTTTGCC TACCCGGCAC
24901 TTAACCTACC CCCCAAGGTT ATGAGCACAG TCATGAGCGA GCTGATCGTG CGCCGTGCAC
24961 GACCCCTGGA GAGGGATGCA AACTTGCAAG AACAAACCGA GGAGGGCCTA CCCGCAGTTG
25021 GCGATGAGCA GCTGGCGCGC TGGCTTGAGA CGCGCGAGCC TGCCGACTTG GAGGAGCGAC
25081 GCAAGCTAAT GATGGCCGCA GTGCTTGTTA CCGTGGAGCT TGAGTGCATG CAGCGGTTCT
25141 TTGCTGACCC GGAGATGCAG CGCAAGCTAG AGGAAACGTT GCACTACACC TTTCGCCAGG

FIG. 7J

25201 GCTACGTGCG CCAGGCCTGC AAAATTTCCA ACGTGGAGCT CTGCAACCTG GTCTCCTACC
25261 TTGGAATTTT GCACGAAAAC CGCCTTGGGC AAAACGTGCT TCATTCCACG CTCAAGGGCG
25321 AGGCGCGCCG CGACTACGTC CGCGACTGCG TTTACTTATT TCTGTGCTAC ACCTGGCAAA
25381 CGGCCATGGG CGTGTGGCAG CAGTGCCTGG AGGAGCGCAA CCTGAAGGAG CTGCAGAAGC
25441 TGCTAAAGCA AAACTTGAAG GACCTATGGA CGGCCTTCAA CGAGCGCTCC GTGGCCGCGC
25501 ACCTGGCGGA CATTATCTTC CCCGAACGCC TGCTTAAAAC CCTGCAACAG GGTCTGCCAG
25561 ACTTCACCAG TCAAAGCATG TTGCAAAACT TTAGGAACTT TATCCTAGAG CGTTCAGGAA
25621 TTCTGCCCGC CACCTGCTGT GCGCTTCCTA GCGACTTTGT GCCCATTAAG TACCGTGAAT
25681 GCCCTCCGCC GCTTTGGGGT CACTGCTACC TTCTGCAGCT AGCCAACTAC CTTGCCTACC
25741 ACTCCGACAT CATGGAAGAC GTGAGCGGTG ACGGCCTACT GGAGTGTCAC TGTCGCTGCA
25801 ACCTATGCAC CCCGCACCGC TCCCTGGTCT GCAATTCACA ACTGCTTAGC GAAAGTCAAA
25861 TTATCGGTAC CTTTGAGCTG CAGGGTCCCT CGCCTGACGA AAAGTCCGCG GCTCCGGGGT
25921 TGAAACTCAC TCCGGGGCTG TGGACGTCGG CTTACCTTCG CAAATTTGTA CCTGAGGACT
25981 ACCACGCCCA CGAGATTAGG TTCTACGAAG ACCAATCCCG CCCGCCAAAT GCGGAGCTTA
26041 CCGCCTGCGT CATTACCCAG GGCCACATCC TTGGCCAATT GCAAGCCATT AACAAAGCCC
26101 GCCAAGAGTT TCTGCTACGA AAGGGACGGG GGGTTTACTT GGACCCCCAG TCCGGCGAGG
26161 AGCTCAACCC AATCCCCCCG CCGCCGCAGC CCTATCAGCA GCCGCGGGCC CTTGCTTCCC
26221 AGGATGGCAC CCAAAAAGAA GCTGCAGCTG CCGCCGCCGC CACCCACGGA CGAGGAGGAA
26281 TACTGGGACA GTCAGGCAGA GGAGGTTTTG GACGAGGAGG AGGAGATGAT GGAAGACTGG
26341 GACAGCCTAG ACGAGGAAGC TTCCGAGGCC GAAGAGGTGT CAGACGAAAC ACCGTCACCC
26401 TCGGTCGCAT TCCCCTCGCC GGCGCCCCAG AAATCGGCAA CCGTTCCCAG CATTGCTACA
26461 ACCTCCGCTC CTCAGGCGCC GCCGGCACTG CCCGTTCGCC GACCCAACCG TAGATGGGAC
26521 ACCACTGGAA CCAGGGCCGG TAAGTCTAAG CAGCCGCCGC CGTTAGCCCA AGAGCAACAA
26581 CAGCGCCAAG GCTACCGCTC GTGGCGCGTG CACAAGAACG CCATAGTTGC TTGCTTGCAA
26641 GACTGTGGGG GCAACATCTC CTTCGCCCGC CGCTTTCTTC TCTACCATCA CGGCGTGGCC
26701 TTCCCCCGTA ACATCCTGCA TTACTACCGT CATCTCTACA GCCCCTACTG CACCGGCGGC
26761 AGCGGCAGCA ACAGCAGCGG CCACGCAGAA GCAAAGGCGA CCGGATAGCA AGACTCTGAC
26821 AAAGCCCAAG AAATCCACAG CGGCGGCAGC AGCAGGAGGA GGAGCACTGC GTCTGGCGCC
26881 CAACGAACCC GTATCGACCC GCGAGCTTAG AAACAGGATT TTTCCCACTC TGTATGCTAT
26941 ATTTCAACAG AGCAGGGGCC AAGAACAAGA GCTGAAAATA AAAAACAGGT CTCTGCGCTC
27001 CCTCACCCGC AGCTGCCTGT ATCACAAAAG CGAAGATCAG CTTCGGCGCA CGCTGGAAGA
27061 CGCGGAGGCT CTCTTCAGCA AATACTGCGC GCTGACTCTT AAGGACTAGT TTCGCGCCCT
27121 TTCTCAAATT TAAGCGCGAA AACTACGTCA TCTCCAGCGG CCACACCCGG CGCCAGCACC
27181 TGTCGTCAGC GCCATTATGA GCAAGGAAAT TCCCACGCCC TACATGTGGA GTTACCAGCC
27241 ACAAATGGGA CTTGCGGCTG GAGCTGCCCA AGACTACTCA ACCCGAATAA ACTACATGAG
27301 CGCGGGACCC CACATGATAT CCCGGGTCAA CGGAATCCGC GCCCACCGAA ACCGAATTCT
27361 CCTCGAACAG GCGGCTATTA CCACCACACC TCGTAATAAC CTTAATCCCC GTAGTTGGCC
27421 CGCTGCCCTG GTGTACCAGG AAAGTCCCGC TCCCACCACT GTGGTACTTC CCAGAGACGC
27481 CCAGGCCGAA GTTCAGATGA CTAACTCAGG GGCGCAGCTT GCGGGCGGCT TTCGTCACAG
27541 GGTGCGGTCG CCCGGGCAGG GTATAACTCA CCTGAAAATC AGAGGGCGAG GTATTCAGCT
27601 CAACGACGAG TCGGTGAGCT CCTCTCTTGG TCTCCGTCCG GACGGGACAT TTCAGATCGG
27661 CGGCGCTGGC CGCTCTTCAT TTACGCCCCG TCAGGCGATC CTAACTCTGC AGACCTCGTC

FIG. 7K

27721 CTCGGAGCCG CGCTCCGGAG GCATTGGAAC TCTACAATTT ATTGAGGAGT TCGTGCCTTC
27781 GGTTTACTTC AACCCCTTTT CTGGACCTCC CGGCCACTAC CCGGACCAGT TTATTCCCAA
27841 CTTTGACGCG GTAAAAGACT CGGCGGACGG CTACGACTGA ATGACCAGTG GAGAGGCAGA
27901 GCAACTGCGC CTGACACACC TCGACCACTG CCGCCGCCAC AAGTGCTTTG CCCGCGGCTC
27961 CGGTGAGTTT TGTTACTTTG AATTGCCCGA AGAGCATATC GAGGGCCCGG CGCACGGCGT
28021 CCGGCTCACC ACCCAGGTAG AGCTTACACG TAGCCTGATT CGGGAGTTTA CCAAGCGCCC
28081 CCTGCTAGTG GAGCGGGAGC GGGGTCCCTG TGTTCTGACC GTGGTTTGCA ACTGTCCTAA
28141 CCCTGGATTA CATCAAGATC TTTGTTGTCA TCTCTGTGCT GAGTATAATA AATACAGAAA
28201 TTAGAATCTA CTGGGGCTCC TGTCGCCATC CTGTGAACGC CACCGTTTTT ACCCACCCAA
28261 AGCAGACCAA AGCAAACCTC ACCTCCGGTT TGCACAAGCG GGCCAATAAG TACCTTACCT
28321 GGTACTTTAA CGGCTCTTCA TTTGTAATTT ACAACAGTTT CCAGCGAGAC GAAGTAAGTT
28381 TGCCACACAA CCTTCTCGGC TTCAACTACA CCGTCAAGAA AAACACCACC ACCACCCTCC
28441 TCACCTGCCG GGAACGTACG AGTGCGTCAC CGGTTGCTGC GCCCACACCT ACAGCCTGAG
28501 CGTAACCAGA CATTACTCCC ATTTTCCCAA AACAGGAGGT GAGCTCAACT CCCGGAACTC
28561 AGGTCAAAAA AGCATTTTGC GGGGTGCTGG GATTTTTTAA TTAAGTATAT GAGCAATTCA
28621 AGTAACTCTA CAAGCTTGTC TAATTTTTCT GGAATTGGGG TCGGGGTTAT CCTTACTCTT
28681 GTAATTCTGT TTATTCTTAT ACTAGCACTT CTGTGCCTTA GGGTTGCCGC CTGCTGCACG
28741 CACGTTTGTA CCTATTGTCA GCTTTTTAAA CGCTGGGGGC GACATCCAAG ATGAGGTACA
28801 TGATTTTAGG CTTGCTCGCC CTTGCGGCAG TCTGCAGCGC TGCCAAAAAG GTTGAGTTTA
28861 AGGAACCAGC TTGCAATGTT ACATTTAAAT CAGAAGCTAA TGAATGCACT ACTCTTATAA
28921 AATGCACCAC AGAACATGAA AAGCTTATTA TTCGCCACAA AGACAAAATT GGCAAGTATG
28981 CTGTATATGC TATTTGGCAG CCAGGTGACA CTAACGACTA TAATGTCACA GTCTTCCAAG
29041 GTGAAAATCG TAAAACTTTT ATGTATAAAT TTCCATTTTA TGAAATGTGC GATATTACCA
29101 TGTACATGAG CAAACAGTAC AAGTTGTGGC CCCCACAAAA GTGTTTAGAG AACACTGGCA
29161 CCTTTTGTTC CACCGCTCTG CTTATTACAG CGCTTGCTTT GGTATGTACC TTACTTTATC
29221 TCAAATACAA AAGCAGACGC AGTTTTATTG ATGAAAAGAA AATGCCTTGA TTTTCCGCTT
29281 GCTTGTATTC CCCTGGACAA TTTACTCTAT GTGGGATATG CGCCAGGCGG GAAAGATTAT
29341 ACCCACAACC TTCAAATCAA ACTTTCCTGG ACGTTAGCGC CTGACTTCTG CCAGCGCCTG
29401 CACTGCAAAT TTGATCAAAC CCAGCTTCAG CTTGCCTGCT CCAGAGATGA CCGGCTCAAC
29461 CATCGCGCCC ACAACGGACT ATCGCAACAC CACTGCTACC GGACTAAAAT CTGCCCTAAA
29521 TTTACCCCAA GTTCATGCCT TTGTCAATGA CTGGGCGAGC TTGGGCATGT GGTGGTTTTC
29581 CATAGCGCTT ATGTTTGTTT GCCTTATTAT TATGTGGCTT ATTTGTTGCC TAAAGCGCAG
29641 ACGCGCCAGA CCCCCCATCT ATAGGCCTAT CATTGTGCTC AACCCACACA ATGAAAAAAT
29701 TCATAGATTG GACGGTCTCA AACCATGTTC TCTTCTTTTA CAGTATGATT AAATGAGACA
29761 TGATTCCTCG AGTCCTTATA TTATTGACCC TTGTTGCGCT TTTCTGTGCG TGCTCTACAT
29821 TGGCTGCGGT CGCTCACATC GAAGTAGATT GCATCCCACC TTTCACAGTT TACCTGCTTT
29881 ACGGATTTGT CACCCTTATC CTCATCTGCA GCCTCGTCAC TGTAGTCATC GCCTTCATTC
29941 AGTTCATTGA CTGGATTTGT GTGCGCATTG CGTACCTTAG GCACCATCCG CAATACAGAG
30001 ACAGGACTAT AGCTGATCTT CTCAGAATTC TTTAATTATG AAACGGATTG TCACTTTTGT
30061 TTTGCTGATT TTCTGCGCCC TACCTGTGCT TTGCTCCCAA ACCTCAGCGC CTCCCAAAAG
30121 ACATATTTCC TGCAGATTCA CTCAAATATG GAACATTCCC AGCTGCTACA ACAAACAGAG
30181 CGATTTGTCA GAAGCCTGGT TATACGCCAT CATCTCTGTC ATGGTTTTTT GCAGTACCAT

FIG. 7L

30241 TTTTGCCCTA GCCATATACC CATACCTTGA CATTGGTTGG AATGCCATAG ATGCCATGAA
30301 CCACCCTACT TTCCCAGCGC CCAATGTCAT ACCACTGCAA CAGGTTATTG CCCCAATCAA
30361 TCAGCCTCGC CCCCCTTCTC CCACCCCCAC TGAGATTAGC TACTTTAATT TGACAGGTGG
30421 AGATGACTGA ATCTCTAGAT CTAGAATTGG ATGGAATTAA CACCGAACAG CGCCTACTAG
30481 AAAGGCGCAA GGCGGCGTCC GAGCGAGAAC GCCTAAAACA AGAAGTTGAA GACATGGTTA
30541 ACCTGCACCA GTGTAAAAGA GGTATCTTTT GTGTGGTCAA GCAGGCCAAA CTTACCTACG
30601 AAAAAACCAC TACCGGCAAC CGCCTTAGCT ACAAGCTACC CACCCAGCGC CAAAAACTGG
30661 TGCTTATGGT GGGAGAAAAA CCTATCACCG TCACCCAGCA CTCGGCAGAA ACAGAAGGCT
30721 GCCTGCACTT CCCCTATCAG GGTCCAGAGG ACCTCTGCAC TCTTATTAAA ACCATGTGTG
30781 GCATTAGAGA TCTTATTCCA TTCAACTAAC AATAAACACA CAATAAATTA CTTACTTAAA
30841 ATCAGTCAGC AAATCTTTGT CCAGCTTATT CAGCATCACC TCCTTTCCCT CCTCCCAACT
30901 CTGGTATTTC AGCAGCCTTT TAGCTGCGAA CTTTCTCCAA AGTCTAAATG GGATGTCAAA
30961 TTCCTCATGT TCTTGTCCCT CCGCACCCAC TATCTTCATA TTGTTGCAGA TGAAACGCGC
31021 CAGACCGTCT GAAGACACCT TCAACCCTGT GTACCCATAT GACACGGAAA CCGGCCCTCC
31081 AACTGTGCCT TTCCTTACCC CTCCCTTTGT GTCGCCAAAT GGGTTCCAAG AAAGTCCCCC
31141 CGGAGTGCTT TCTTTGCGTC TTTCAGAACC TTTGGTTACC TCACACGGCA TGCTTGCGCT
31201 AAAAATGGGC AGCGGCCTGT CCCTGGATCA GGCAGGCAAC CTTACATCAA ATACAATCAC
31261 TGTTTCTCAA CCGCTAAAAA AAACAAAGTC CAATATAACT TTGGAAACAT CCGCGCCCCT
31321 TACAGTCAGC TCAGGCGCCC TAACCATGGC CACAACTTCG CCTTTGGTGG TCTCTGACAA
31381 CACTCTTACC ATGCAATCAC AAGCACCGCT AACCGTGCAA GACTCAAAAC TTAGCATTGC
31441 TACCAAAGAG CCACTTACAG TGTTAGATGG AAAACTGGCC CTGCAGACAT CAGCCCCCCT
31501 CTCTGCCACT GATAACAACG CCCTCACTAT CACTGCCTCA CCTCCTCTTA CTACTGCAAA
31561 TGGTAGTCTG GCTGTTACCA TGGAAAACCC ACTTTACAAC AACAATGGAA AACTTGGGCT
31621 CAAAATTGGC GGTCCTTTGC AAGTGGCCAC CGACTCACAT GCACTAACAC TAGGTACTGG
31681 TCAGGGGGTT GCAGTTCATA ACAATTTGCT ACATACAAAA GTTACAGGCG CAATAGGGTT
31741 TGATACATCT GGCAACATGG AACTTAAAAC TGGAGATGGC CTCTATGTGG ATAGCGCCGG
31801 TCCTAACCAA AAACTACATA TTAATCTAAA TACCACAAAA GGCCTTGCTT TTGACAACAC
31861 CGCAATAACA ATTAACGCTG GAAAAGGGTT GGAATTTGAA ACAGACTCCT CAAACGGAAA
31921 TCCCATAAAA ACAAAAATTG GATCAGGCAT ACAATATAAT ACCAATGGAG CTATGGTTGC
31981 AAAACTTGGA ACAGGCCTCA GTTTTGACAG CTCCGGAGCC ATAACAATGG GCAGCATAAA
32041 CAATGACAGA CTTACTCTTT GGACAACACC AGACCCATCC CCAAATTGCA GAATTGCTTC
32101 AGATAAAGAC TGCAAGCTAA CTCTGGCGCT AACAAAATGT GGCAGTCAAA TTTTGGGCAC
32161 TGTTTCAGCT TTGGCAGTAT CAGGTAATAT GGCCTCCATC AATGGAACTC TAAGCAGTGT
32221 AAACTTGGTT CTTAGATTTG ATGACAACGG AGTGCTTATG TCAAATTCAT CACTGGACAA
32281 ACAGTATTGG AACTTTAGAA ACGGGGACTC CACTAACGGT CAACCATACA CTTATGCTGT
32341 TGGGTTTATG CCAAACCTAA AAGCTTACCC AAAAACTCAA AGTAAAACTG CAAAAAGTAA
32401 TATTGTTAGC CAGGTGTATC TTAATGGTGA CAAGTCTAAA CCATTGCATT TTACTATTAC
32461 GCTAAATGGA ACAGATGAAA CCAACCAAGT AAGCAAATAC TCAATATCAT TCAGTTGGTC
32521 CTGGAACAGT GGACAATACA CTAATGACAA ATTTGCCACC AATTCCTATA CCTTCTCCTA
32581 CATTGCCCAG GAATAAAGAA TCGTGAACCT GTTGCATGTT ATGTTTCAAC GTGTTTATTT
32641 TTCAATTGCA GAAAATTTCA AGTCATTTTT CATTCAGTAG TATAGCCCCA CCACCACATA
32701 GCTTATACTA ATCACCGTAC CTTAATCAAA CTCACAGAAC CCTAGTATTC AACCTGCCAC

FIG. 7M

32761 CTCCCTCCCA ACACACAGAG TACACAGTCC TTTCTCCCCG GCTGGCCTTA AACAGCATCA
32821 TATCATGGGT AACAGACATA TTCTTAGGTG TTATATTCCA CACGGTCTCC TGTCGAGCCA
32881 AACGCTCATC AGTGATGTTA ATAAACTCCC CGGGCAGCTC GCTTAAGTTC ATGTCGCTGT
32941 CCAGCTGCTG AGCCACAGGC TGCTGTCCAA CTTGCGGTTG CTCAACGGGC GGCGAAGGAG
33001 AAGTCCACGC CTACATGGGG GTAGAGTCAT AATCGTGCAT CAGGATAGGG CGGTGGTGCT
33061 GCAGCAGCGC GCGAATAAAC TGCTGCCGCC GCCGCTCCGT CCTGCAGGAA TACAACATGG
33121 CAGTGGTCTC CTCAGCGATG ATTCGCACCG CCCGCAGCAT AAGGCGCCTT GTCCTCCGGG
33181 CACAGCAGCG CACCCTGATC TCACTTAAGT CAGCACAGTA ACTGCAGCAC AGTACCACAA
33241 TATTGTTTAA AATCCCACAG TGCAAGGCGC TGTATCCAAA GCTCATGGCG GGGACCACAG
33301 AACCCACGTG GCCATCATAC CACAAGCGCA GGTAGATTAA GTGGCGACCC CTCATAAACA
33361 CGCTGGACAT AAACATTACC TCTTTTGGCA TGTTGTAATT CACCACCTCC CGGTACCATA
33421 TAAACCTCTG ATTAAACATG GCGCCATCCA CCACCATCCT AAACCAGCTG GCCAAAACCT
33481 GCCCGCCGGC TATGCACTGC AGGGAACCGG GACTGGAACA ATGACAGTGG AGAGCCCAGG
33541 ACTCGTAACC ATGGATCATC ATGCTCGTCA TGATATCAAT GTTGGCACAA CACAGGCACA
33601 CGTGCATACA CTTCCTCAGG ATTACAAGCT CCTCCCGCGT CAGAACCATA TCCCAGGGAA
33661 CAACCCATTC CTGAATCAGC GTAAATCCCA CACTGCAGGG AAGACCTCGC ACGTAACTCA
33721 CGTTGTGCAT TGTCAAAGTG TTACATTCGG GCAGCAGCGG ATGATCCTCC AGTATGGTAG
33781 CGCGTGTCTC TGTCTCAAAA GGAGGTAGGC GATCCCTACT GTACGGAGTG CGCCGAGACA
33841 ACCGAGATCG TGTTGGTCGT AGTGTCATGC CAAATGGAAC GCCGGACGTA GTCATATTTC
33901 CTGAAGCAAA ACCAGGTGCG GGCGTGACAA ACAGATCTGC GTCTCCGGTC TCGTCGCTTA
33961 GCTCGCTCTG TGTAGTAGTT GTAGTATATC CACTCTCTCA AAGCATCCAG GCGCCCCCTG
34021 GCTTCGGGTT CTATGTAAAC TCCTTCATGC GCCGCTGCCC TGATAACATC CACCACCGCA
34081 GAATAAGCCA CACCCAGCCA ACCTACACAT TCGTTCTGCG AGTCACACAC GGGAGGAGCG
34141 GGAAGAGCTG GAAGAACCAT GTTTTTTTTT TTTATTCCAA AAGATTATCC AAAACCTCAA
34201 AATGAAGATC TATTAAGTGA ACGCGCTCCC CTCCGGTGGC GTGGTCAAAC TCTACAGCCA
34261 AAGAACAGAT AATGGCATTT GTAAGATGTT GCACAATGGC TTCCAAAAGG CAAACTGCCC
34321 TCACGTCCAA GTGGACGTAA AGGCTAAACC CTTCAGGGTG AATCTCCTCT ATAAACATTC
34381 CAGCACCTTC AACCATGCCC AAATAATTTT CATCTCGCCA CCTTATCAAT ATGTCTCTAA
34441 GCAAATCCCG AATATTAAGT CCGGCCATTG TAAAAATCTG CTCCAGAGCG CCCTCCACCT
34501 TCAGCCTCAA GCAGCGAATC ATGATTGCAA AAATTCAGGT TCCTCACAGA CCTGTATAAG
34561 ATTCAAAAGC GGAACATTAA CAAAAATACC GCGATCCCGT AGGTCCCTTC GCAGGGCCAG
34621 CTGAACATAA TCGTGCAGGT CTGCACGGAC CAGCGCGGCC ACTTCCCCGC CAGGAACCAT
34681 GACAAAAGAA CCCACACTGA TTATGACACG CATACTCGGA GCTATGCTAA CCAGCGTAGC
34741 CCCGATGTAA GCTTGTTGCA TGGGCGGCGA TATAAAATGC AAGGTACTGC TCAAAAAATC
34801 AGGCAAAGCC TCGCGCAAAA AAGCAAGCAC ATCGTAGTCA TGCTCATGCA GATAAAGGCA
34861 GGTAAGTTCC GGAACCACCA CAGAAAAAGA CACCATTTTT CTCTCAAACA TGTCTGCGGG
34921 TTCCTGCATA AACACAAAAT AAAATAACAA AAAAAAAAAA ACATTTAAAC ATTAGAAGCC
34981 TGTNTTACAA CAGGAAAAAC AACCCTTATA AGCATAAGAC GGACTACGGC CATGCCGGCG
35041 TGACCGTAAA AAAACTGGTC ACCGTGATTA AAAAGCACCA CCGACAGTTC CTCGGTCATG
35101 TCCGGAGTCA TAATGTAAGA CTCGGTAAAC ACATCAGGTT GGTTAACATC GGTCAGTGCT
35161 AAAAAGCGAC CGAAATAGCC CGGGGGAATA CATACCCGCA GGCGTAGAGA CAACATTACA
35221 GCCCCCATAG GAGGTATAAC AAAATTAATA GGAGAGAAAA ACACATAAAC ACCTGAAAAA

FIG. 7N

35281 CCCTCCTGCC TAGGCAAAAT AGCACCCTCC CGCTCCAGAA CAACATACAG CGCTTCCACA
35341 GCGGCAGCCA TAACAGTCAG CCTTACCAGT AAAAAAACCT ATTAAAAAAC ACCACTCGAC
35401 ACGGCACCAG CTCAATCAGT CACAGTGTAA AAAGGGCCAA GTACAGAGCG AGTATATATA
35461 GGACTAAAAA ATGACGTAAC GGTTAAAGTC CACAAAAACC ACCCAGAAAA CCGCACGCGA
35521 ACCTACGCCC AGAAACGAAA GCCAAAAAAC CCACAACTTC CTCAAATCTT CACTTCCGTT
35581 TTCCCACGAT ACGTCACTTC CCATTTTAAA AAAAAACTAC AATTCCCAAT ACATGCAAGT
35641 TACTCCGCCC TAAAACCTAC GTCACCCGCC CCGTTCCCAC GCCCCGCGCC ACGTCACAAA
35701 CTCCACCCCC TCATTATCAT ATTGGCTTCA ATCCAAAATA AGGTATATTA TTGATGATG

FIG. 7O

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   1 CATCATCAAT AATATACCTT ATTTTGGATT GAAGCCAATA TGATAATGAG GGGGTGGAGT
  61 TTGTGACGTG GCGCGGGGCG TGGGAACGGG GCGGGTGACG TAGTAGTGTG GCGGAAGTGT
 121 GATGTTGCAA GTGTGGCGGA ACACATGTAA GCGACGGATG TGGCAAAAGT GACGTTTTTG
 181 GTGTGCGCCG GTGTACACAG GAAGTGACAA TTTTCGCGCG GTTTTAGGCG GATGTTGTAG
 241 TAAATTTGGG CGTAACCGAG TAAGATTTGG CCATTTTCGC GGGAAAACTG AATAAGAGGA
 301 AGTGAAATCT GAATAATTTT GTGTTACTCA TAGCGCGTAA TATTTGTCTA GGGCCGCGGG
 361 GACTTTGACC GTTTACGTGG AGACTCGCCC AGGTGTTTTT CTCAGGTGTT TTCCGCGTTC
 421 CGGGTCAAAG TTGGCGTTTT ATTATTATAG TCAGCTGACG TGTAGTGTAT TTATACCCGG
 481 TGAGTTCCTC AAGAGGCCAC TCTTGAGTGC CAGCGAGTAG AGTTTTCTCC TCCGAGCCGC
 541 TCCGACACCG GGACTGAAAA TGAGACATAT TATCTGCCAC GGAGGTGTTA TTACCGAAGA
 601 AATGGCCGCC AGTCTTTTGG ACCAGCTGAT CGAAGAGGTA CTGGCTGATA ATCTTCCACC
 661 TCCTAGCCAT TTTGAACCAC CTACCCTTCA CGAACTGTAT GATTTAGACG TGACGGCCCC
 721 CGAAGATCCC AACGAGGAGG CGGTTTCGCA GATTTTTCCC GACTCTGTAA TGTTGGCGGT
 781 GCAGGAAGGG ATTGACTTAC TCACTTTTCC GCCGGCGCCC GGTTCTCCGG AGCCGCCTCA
 841 CCTTTCCCGG CAGCCCGAGC AGCCGGAGCA GAGAGCCTTG GGTCCGGTTT CTATGCCAAA
 901 CCTTGTACCG GAGGTGATCG ATCTTACCTG CCACGAGGCT GGCTTTCCAC CCAGTGACGA
 961 CGAGGATGAA GAGGGTGAGG AGTTTGTGTT AGATTATGTG GAGCACCCCG GGCACGGTTG
1021 CAGGTCTTGT CATTATCACC GGAGGAATAC GGGGGACCCA GATATTATGT GTTCGCTTTG
1081 CTATATGAGG ACCTGTGGCA TGTTTGTCTA CAGTAAGTGA AAATTATGGG CAGTGGGTGA
1141 TAGAGTGGTG GGTTTGGTGT GGTAATTTTT TTTTTAATTT TTACAGTTTT GTGGTTTAAA
1201 GAATTTTGTA TTGTGATTTT TTTAAAAGGT CCTGTGTCTG AACCTGAGCC TGAGCCCGAG
1261 CCAGAACCGG AGCCTGCAAG ACCTACCCGC CGTCCTAAAA TGGCGCCTGC TATCCTGAGA
1321 CGCCCGACAT CACCTGTGTC TAGAGAATGC AATAGTAGTA CGGATAGCTG TGACTCCGGT
1381 CCTTCTAACA CACCTCCTGA GATACACCCG GTGGTCCCGC TGTGCCCCAT TAAACCAGTT
1441 GCCGTGAGAG TTGGTGGGCG TCGCCAGGCT GTGGAATGTA TCGAGGACTT GCTTAACGAG
1501 CCTGGGCAAC CTTTGGACTT GAGCTGTAAA CGCCCCAGGC CATAAGGTGT AAACCTGTGA
1561 TTGCGTGTGT GGTTAACGCC TTTGTTTGCT GAATGAGTTG ATGTAAGTTT AATAAAGGGT
1621 GAGATAATGT TTAACTTGCA TGGCGTGTTA AATGGGGCGG GGCTTAAAGG GTATATAATG
1681 CGCCGTGGGC TAATCTTGGT TACATCTGAC CTCATGGAGG CTTGGGAGTG TTTGGAAGAT
1741 TTTTCTGCTG TGCGTAACTT GCTGGAACAG AGCTCTAACA GTACCTCTTG GTTTTGGAGG
1801 TTTCTGTGGG GCTCATCCCA GGCAAAGTTA GTCTGCAGAA TTAAGGAGGA TTACAAGTGG
1861 GAATTTGAAG AGCTTTTGAA ATCCTGTGGT GAGCTGTTTG ATTCTTTGAA TCTGGGTCAC
1921 CAGGCGCTTT TCCAAGAGAA GGTCATCAAG ACTTTGGATT TTTCCACACC GGGGCGCGCT
1981 GCGGCTGCTG TTGCTTTTTT GAGTTTTATA AAGGATAAAT GGAGCGAAGA AACCCATCTG
2041 AGCGGGGGGT ACCTGCTGGA TTTTCTGGCC ATGCATCTGT GGAGAGCGGT TGTGAGACAC
2101 AAGAATCGCC TGCTACTGTT GTCTTCCGTC CGCCCGGCGA TAATACCGAC GGAGGAGCAG
2161 CAGCAGCAGC AGGAGGAAGC CAGGCGGCGG CGGCAGGAGC AGAGCCCATG GAACCCGAGA
2221 GCCGGCCTGG ACCCTCGGGA ATGAATGTTG TACAGGTGGC TGAACTGTAT CCAGAACTGA
2281 GACGCATTTT GACAATTACA GAGGATGGGC AGGGGCTAAA GGGGGTAAAG AGGGAGCGGG
2341 GGGCTTGTGA GGCTACAGAG GAGGCTAGGA ATCTAGCTTT TAGCTTAATG ACCAGACACC
2401 GTCCTGAGTG TATTACTTTT CAACAGATCA AGGATAATTG CGCTAATGAG CTTGATCTGC
2461 TGGCGCAGAA GTATTCCATA GAGCAGCTGA CCACTTACTG GCTGCAGCCA GGGGATGATT
2521 TTGAGGAGGC TATTAGGGTA TATGCAAAGG TGGCACTTAG GCCAGATTGC AAGTACAAGA
2581 TCAGCAAACT TGTAAATATC AGGAATTGTT GCTACATTTC TGGGAACGGG GCCGAGGTGG
2641 AGATAGATAC GGAGGATAGG GTGGCCTTTA GATGTAGCAT GATAAATATG TGGCCGGGGG
2701 TGCTTGGCAT GGACGGGGTG GTTATTATGA ATGTAAGGTT TACTGGCCCC AATTTTAGCG
2761 GTACGGTTTT CCTGGCCAAT ACCAACCTTA TCCTACACGG TGTAAGCTTC TATGGGTTTA
2821 ACAATACCTG TGTGGAAGCC TGGACCGATG TAAGGGTTCG GGGCTGTGCC TTTTACTGCT
2881 GCTGGAAGGG GGTGGTGTGT CGCCCCAAAA GCAGGGCTTC AATTAAGAAA TGCCTCTTTG
2941 AAAGGTGTAC CTTGGGTATC CTGTCTGAGG GTAACTCCAG GGTGCGCCAC AATGTGGCCT
3001 CCGACTGTGG TTGCTTCATG CTAGTGAAAA GCGTGGCTGT GATTAAGCAT AACATGGTAT
3061 GTGGCAACTG CGAGGACAGG GCCTCTCAGA TGCTGACCTG CTCGGACGGC AACTGTCACC
3121 TGCTGAAGAC CATTCACGTA GCCAGCCACT CTCGCAAGGC CTGGCCAGTG TTTGAGCATA
3181 ACATACTGAC CCGCTGTTCC TTGCATTTGG GTAACAGGAG GGGGGTGTTC CTACCTTACC
3241 AATGCAATTT GAGTCACACT AAGATATTGC TTGAGCCCGA GAGCATGTCC AAGGTGAACC
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FIG. 8A

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3301 TGAACGGGGT GTTTGACATG ACCATGAAGA TCTGGAAGGT GCTGAGGTAC GATGAGACCC
3361 GCACCAGGTG CAGACCCTGC GAGTGTGGCG GTAAACATAT TAGGAACCAG CCTGTGATGC
3421 TGGATGTGAC CGAGGAGCTG AGGCCCGATC ACTTGGTGCT GGCCTGCACC CGCGCTGAGT
3481 TTGGCTCTAG CGATGAAGAT ACAGATTGAG GTACTGAAAT GTGTGGGCGT GGCTTAAGGG
3541 TGGGAAAGAA TATATAAGGT GGGGGTCTTA TGTAGTTTTG TATCTGTTTT GCAGCAGCCG
3601 CCGCCGCCAT GAGCACCAAC TCGTTTGATG GAAGCATTGT GAGCTCATAT TTGACAACGC
3661 GCATGCCCCC ATGGGCCGGG GTGCGTCAGA ATGTGATGGG CTCCAGCATT GATGGTCGCC
3721 CCGTCCTGCC CGCAAACTCT ACTACCTTGA CCTACGAGAC CGTGTCTGGA ACGCCGTTGG
3781 AGACTGCAGC CTCCGCCGCC GCTTCAGCCG CTGCAGCCAC CGCCCGCGGG ATTGTGACTG
3841 ACTTTGCTTT CCTGAGCCCG CTTGCAAGCA GTGCAGCTTC CCGTTCATCC GCCCGCGATG
3901 ACAAGTTGAC GGCTCTTTTG GCACAATTGG ATTCTTTGAC CCGGGAACTT AATGTCGTTT
3961 CTCAGCAGCT GTTGGATCTG CGCCAGCAGG TTTCTGCCCT GAAGGCTTCC TCCCCTCCCA
4021 ATGCGGTTTA AAACATAAAT AAAAAACCAG ACTCTGTTTG GATTTGGATC AAGCAAGTGT
4081 CTTGCTGTCT TTATTTAGGG GTTTTGCGCG CGCGGTAGGC CCGGGACCAG CGGTCTCGGT
4141 CGTTGAGGGT CCTGTGTATT TTTTCCAGGA CGTGGTAAAG GTGACTCTGG ATGTTCAGAT
4201 ACATGGGCAT AAGCCCGTCT CTGGGGTGGA GGTAGCACCA CTGCAGAGCT TCATGCTGCG
4261 GGGTGGTGTT GTAGATGATC CAGTCGTAGC AGGAGCGCTG GGCGTGGTGC CTAAAAATGT
4321 CTTTCAGTAG CAAGCTGATT GCCAGGGGCA GGCCCTTGGT GTAAGTGTTT ACAAAGCGGT
4381 TAAGCTGGGA TGGGTGCATA CGTGGGGATA TGAGATGCAT CTTGGACTGT ATTTTTAGGT
4441 TGGCTATGTT CCCAGCCATA TCCCTCCGGG GATTCATGTT GTGCAGAACC ACCAGCACAG
4501 TGTATCCGGT GCACTTGGGA AATTTGTCAT GTAGCTTAGA AGGAAATGCG TGGAAGAACT
4561 TGGAGACGCC CTTGTGACCT CCAAGATTTT CCATGCATTC GTCCATAATG ATGGCAATGG
4621 GCCCACGGGC GGCGGCCTGG GCGAAGATAT TTCTGGGATC ACTAACGTCA TAGTTGTGTT
4681 CCAGGATGAG ATCGTCATAG GCCATTTTTA CAAAGCGCGG GCGGAGGGTG CCAGACTGCG
4741 GTATAATGGT TCCATCCGGC CCAGGGGCGT AGTTACCCTC ACAGATTTGC ATTTCCCACG
4801 CTTTGAGTTC AGATGGGGGG ATCATGTCTA CCTGCGGGGC GATGAAGAAA ACGGTTTCCG
4861 GGGTAGGGGA GATCAGCTGG GAAGAAAGCA GGTTCCTGAG CAGCTGCGAC TTACCGCAGC
4921 CGGTGGGCCC GTAAATCACA CCTATTACCG GGTGCAACTG GTAGTTAAGA GAGCTGCAGC
4981 TGCCGTCATC CCTGAGCAGG GGGGCCACTT CGTTAAGCAT GTCCCTGACT CGCATGTTTT
5041 CCCTGACCAA ATCCGCCAGA AGGCGCTCGC CGCCCAGCGA TAGCAGTTCT TGCAAGGAAG
5101 CAAAGTTTTT CAACGGTTTG AGACCGTCCG CCGTAGGCAT GCTTTTGAGC GTTTGACCAA
5161 GCAGTTCCAG GCGGTCCCAC AGCTCGGTCA CCTGCTCTAC GGCATCTCGA TCCAGCATAT
5221 CTCCTCGTTT CGCGGGTTGG GGCGGCTTTC GCTGTACGGC AGTAGTCGGT GCTCGTCCAG
5281 ACGGGCCAGG GTCATGTCTT TCCACGGGCG CAGGGTCCTC GTCAGCGTAG TCTGGGTCAC
5341 GGTGAAGGGG TGCGCTCCGG GCTGCGCGCT GGCCAGGGTG CGCTTGAGGC TGGTCCTGCT
5401 GGTGCTGAAG CGCTGCCGGT CTTCGCCCTG CGCGTCGGCC AGGTAGCATT TGACCATGGT
5461 GTCATAGTCC AGCCCCTCCG CGGCGTGGCC CTTGGCGCGC AGCTTGCCCT TGGAGGAGGC
5521 GCCGCACGAG GGGCAGTGCA GACTTTTGAG GGCGTAGAGC TTGGGCGCGA GAAATACCGA
5581 TTCCGGGGAG TAGGCATCCG CGCCGCAGGC CCCGCAGACG GTCTCGCATT CCACGAGCCA
5641 GGTGAGCTCT GGCCGTTCGG GGTCAAAAAC CAGGTTTCCC CCATGCTTTT TGATGCGTTT
5701 CTTACCTCTG GTTTCCATGA GCCGGTGTCC ACGCTCGGTG ACGAAAAGGC TGTCCGTGTC
5761 CCCGTATACA GACTTGAGAG GCCTGTCCTC GAGCGGTGTT CCGCGGTCCT CCTCGTATAG
5821 AAACTCGGAC CACTCTGAGA CAAAGGCTCG CGTCCAGGCC AGCACGAAGG AGGCTAAGTG
5881 GGAGGGGTAG CGGTCGTTGT CCACTAGGGG GTCCACTCGC TCCAGGGTGT GAAGACACAT
5941 GTCGCCCTCT TCGGCATCAA GGAAGGTGAT TGGTTTGTAG GTGTAGGCCA CGTGACCGGG
6001 TGTTCCTGAA GGGGGGCTAT AAAAGGGGGT GGGGGCGCGT TCGTCCTCAC TCTCTTCCGC
6061 ATCGCTGTCT GCGAGGGCCA GCTGTTGGGG TGAGTACTCC CTCTGAAAAG CGGGCATGAC
6121 TTCTGCGCTA AGATTGTCAG TTTCCAAAAA CGAGGAGGAT TTGATATTCA CCTGGCCCGC
6181 GGTGATGCCT TTGAGGGTGG CCGCATCCAT CTGGTCAGAA AAGACAATCT TTTTGTTGTC
6241 AAGCTTGGTG GCAAACGACC CGTAGAGGGC GTTGGACAGC AACTTGGCGA TGGAGCGCAG
6301 GGTTTGGTTT TTGTCGCGAT CGGCGCGCTC CTTGGCCGCG ATGTTTAGCT GCACGTATTC
6361 GCGCGCAACG CACCGCCATT CGGGAAAGAC GGTGGTGCGC TCGTCGGGCA CCAGGTGCAC
6421 GCGCCAACCG CGGTTGTGCA GGGTGACAAG GTCAACGCTG GTGGCTACCT CTCCGCGTAG
6481 GCGCTCGTTG GTCCAGCAGA GGCGGCCGCC CTTGCGCGAG CAGAATGGCG GTAGGGGGTC
6541 TAGCTGCGTC TCGTCCGGGG GGTCTGCGTC CACGGTAAAG ACCCCGGGCA GCAGGCGCGC
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FIG. 8B

6601 GTCGAAGTAG TCTATCTTGC ATCCTTGCAA GTCTAGCGCC TGCTGCCATG CGCGGGCGGC
6661 AAGCGCGCGC TCGTATGGGT TGAGTGGGGG ACCCCATGGC ATGGGGTGGG TGAGCGCGGA
6721 GGCGTACATG CCGCAAATGT CGTAAACGTA GAGGGGCTCT CTGAGTATTC CAAGATATGT
6781 AGGGTAGCAT CTTCCACCGC GGATGCTGGC GCGCACGTAA TCGTATAGTT CGTGCGAGGG
6841 AGCGAGGAGG TCGGGACCGA GGTTGCTACG GGCGGGCTGC TCTGCTCGGA AGACTATCTG
6901 CCTGAAGATG GCATGTGAGT TGGATGATAT GGTTGGACGC TGGAAGACGT TGAAGCTGGC
6961 GTCTGTGAGA CCTACCGCGT CACGCACGAA GGAGGCGTAG GAGTCGCGCA GCTTGTTGAC
7021 CAGCTCGGCG GTGACCTGCA CGTCTAGGGC GCAGTAGTCC AGGGTTTCCT TGATGATGTC
7081 ATACTTATCC TGTCCCTTTT TTTTCCACAG CTCGCGGTTG AGGACAAACT CTTCGCGGTC
7141 TTTCCAGTAC TCTTGGATCG GAAACCCGTC GGCCTCCGAA CGGTAAGAGC CTAGCATGTA
7201 GAACTGGTTG ACGGCCTGGT AGGCGCAGCA TCCCTTTTCT ACGGGTAGCG CGTATGCCTG
7261 CGCGGCCTTC CGGAGCGAGG TGTGGGTGAG CGCAAAGGTG TCCCTGACCA TGACTTTGAG
7321 GTACTGGTAT TTGAAGTCAG TGTCGTCGCA TCCGCCCTGC TCCCAGAGCA AAAAGTCCGT
7381 GCGCTTTTTG GAACGCGGAT TTGGCAGGGC GAAGGTGACA TCGTTGAAGA GTATCTTTCC
7441 CGCGCGAGGC ATAAAGTTGC GTGTGATGCG GAAGGGTCCC GGCACCTCGG AACGGTTGTT
7501 AATTACCTGG GCGGCGAGCA CGATCTCGTC AAAGCCGTTG ATGTTGTGGC CCACAATGTA
7561 AAGTTCCAAG AAGCGCGGGA TGCCCTTGAT GGAAGGCAAT TTTTTAAGTT CCTCGTAGGT
7621 GAGCTCTTCA GGGGAGCTGA GCCCGTGCTC TGAAAGGGCC CAGTCTGCAA GATGAGGGTT
7681 GGAAGCGACG AATGAGCTCC ACAGGTCACG GGCCATTAGC ATTTGCAGGT GGTCGCGAAA
7741 GGTCCTAAAC TGGCGACCTA TGGCCATTTT TTCTGGGGTG ATGCAGTAGA AGGTAAGCGG
7801 GTCTTGTTCC CAGCGGTCCC ATCCAAGGTT CGCGGCTAGG TCTCGCGCGG CAGTCACTAG
7861 AGGCTCATCT CCGCCGAACT TCATGACCAG CATGAAGGGC ACGAGCTGCT TCCCAAAGGC
7921 CCCCATCCAA GTATAGGTCT CTACATCGTA GGTGACAAAG AGACGCTCGG TGCGAGGATG
7981 CGAGCCGATC GGGAAGAACT GGATCTCCCG CCACCAATTG GAGGAGTGGC TATTGATGTG
8041 GTGAAAGTAG AAGTCCCTGC GACGGGCCGA ACACTCGTGC TGGCTTTTGT AAAAACGTGC
8101 GCAGTACTGG CAGCGGTGCA CGGGCTGTAC ATCCTGCACG AGGTTGACCT GACGACCGCG
8161 CACAAGGAAG CAGAGTGGGA ATTTGAGCCC CTCGCCTGGC GGGTTTGGCT GGTGGTCTTC
8221 TACTTCGGCT GCTTGTCCTT GACCGTCTGG CTGCTCGAGG GGAGTTACGG TGGATCGGAC
8281 CACCACGCCG CGCGAGCCCA AAGTCCAGAT GTCCGCGCGC GGCGGTCGGA GCTTGATGAC
8341 AACATCGCGC AGATGGGAGC TGTCCATGGT CTGGAGCTCC CGCGGCGTCA GGTCAGGCGG
8401 GAGCTCCTGC AGGTTTACCT CGCATAGACG GGTCAGGGCG CGGGCTAGAT CCAGGTGATA
8461 CCTAATTTCC AGGGGCTGGT TGGTGGCGGC GTCGATGGCT TGCAAGAGGC CGCATCCCCG
8521 CGGCGCGACT ACGGTACCGC GCGGCGGGCG GTGGGCCGCG GGGGTGTCCT TGGATGATGC
8581 ATCTAAAAGC GGTGACGCGG GCGAGCCCCC GGAGGTAGGG GGGCTCCGG ACCCGCCGGG
8641 AGAGGGGGCA GGGGCACGTC GGCGCCGCGC GCGGGCAGGA GCTGGTGCTG CGCGCGTAGG
8701 TTGCTGGCGA ACGCGACGAC GCGGCGGTTG ATCTCCTGAA TCTGGCGCCT CTGCGTGAAG
8761 ACGACGGGCC CGGTGAGCTT GAGCCTGAAA GAGAGTTCGA CAGAATCAAT TTCGGTGTCG
8821 TTGACGGCGG CCTGGCGCAA AATCTCCTGC ACGTCTCCTG AGTTGTCTTG ATAGGCGATC
8881 TCGGCCATGA ACTGCTCGAT CTCTTCCTCC TGGAGATCTC CGCGTCCGGC TCGCTCCACG
8941 GTGGCGGCGA GGTCGTTGGA AATGCGGGCC ATGAGCTGCG AGAAGGCGTT GAGGCCTCCC
9001 TCGTTCCAGA CGCGGCTGTA GACCACGCCC CCTTCGGCAT CGCGGGCGCG CATGACCACC
9061 TGCGCGAGAT TGAGCTCCAC GTGCCGGGCG AAGACGGCGT AGTTTCGCAG GCGCTGAAAG
9121 AGGTAGTTGA GGGTGGTGGC GGTGTGTTCT GCCACGAAGA AGTACATAAC CCAGCGTCGC
9181 AACGTGGATT CGTTGATATC CCCCAAGGCC TCAAGGCGCT CCATGGCCTC GTAGAAGTCC
9241 ACGGCGAAGT TGAAAAACTG GGAGTTGCGC GCCGACACGG TTAACTCCTC CTCCAGAAGA
9301 CGGATGAGCT CGGCGACAGT GTCGCGCACC TCGCGCTCAA AGGCTACAGG GGCCTCTTCT
9361 TCTTCTTCAA TCTCCTCTTC CATAAGGGCC TCCCCTTCTT CTTCTTCTGG CGGCGGTGGG
9421 GGAGGGGGGA CACGGCGGCG ACGACGGCGC ACCGGGAGGC GGTCGACAAA GCGCTCGATC
9481 ATCTCCCCGC GGCGACGGCG CATGGTCTCG GTGACGGCGC GGCCGTTCTC GCGGGGGCGC
9541 AGTTGGAAGA CGCCGCCCGT CATGTCCCGG TTATGGGTTG GCGGGGGGCT GCCATGCGGC
9601 AGGGATACGG CGCTAACGAT GCATCTCAAC AATTGTTGTG TAGGTACTCC GCCGCCGAGG
9661 GACCTGAGCG AGTCCGCATC GACCGGATCG GAAAACCTCT CGAGAAAGGC GTCTAACCAG
9721 TCACAGTCGC AAGGTAGGCT GAGCACCGTG GCGGGCGGCA GCGGGCGGCG GTCGGGGTTG
9781 TTTCTGGCGG AGGTGCTGCT GATGATGTAA TTAAAGTAGG CGGTCTTGAG ACGGCGGATG
9841 GTCGACAGAA GCACCATGTC CTTGGGTCCG GCCTGCTGAA TGCGCAGGCG GTCGGCCATG

FIG. 8C

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 9901 CCCCAGGCTT CGTTTTGACA TCGGCGCAGG TCTTTGTAGT AGTCTTGCAT GAGCCTTTCT
 9961 ACCGGCACTT CTTCTTCTCC TTCCTCTTGT CCTGCATCTC TTGCATCTAT CGCTGCGGCG
10021 GCGGCGGAGT TTGGCCGTAG GTGGCGCCCT CTTCCTCCCA TGCGTGTGAC CCCGAAGCCC
10081 CTCATCGGCT GAAGCAGGGC TAGGTCGGCG ACAACGCGCT CGGCTAATAT GGCCTGCTGC
10141 ACCTGCGTGA GGGTAGACTG GAAGTCATCC ATGTCCACAA AGCGGTGGTA TGCGCCCGTG
10201 TTGATGGTGT AAGTGCAGTT GGCCATAACG GACCAGTTAA CGGTCTGGTG ACCCGGCTGC
10261 GAGAGCTCGG TGTACCTGAG ACGCGAGTAA GCCCTCGAGT CAAATACGTA GTCGTTGCAA
10321 GTCCGCACCA GGTACTGGTA TCCCACCAAA AAGTGCGGCG GCGGCTGGCG GTAGAGGGGC
10381 CAGCGTAGGG TGGCCGGGGC TCCGGGGGCG AGATCTTCCA ACATAAGGCG ATGATATCCG
10441 TAGATGTACC TGGACATCCA GGTGATGCCG GCGGCGGTGG TGGAGGCGCG CGGAAAGTCG
10501 CGGACGCGGT TCCAGATGTT GCGCAGCGGC AAAAAGTGCT CCATGGTCGG GACGCTCTGG
10561 CCGGTCAGGC GCGCGCAATC GTTGACGCTC TAGACCGTGC AAAAGGAGAG CCTGTAAGCG
10621 GGCACTCTTC CGTGGTCTGG TGGATAAATT CGCAAGGGTA TCATGGCGGA CGACCGGGGT
10681 TCGAGCCCCG TATCCGGCCG TCCGCCGTGA TCCATGCGGT TACCGCCCGC GTGTCGAACC
10741 CAGGTGTGCG ACGTCAGACA ACGGGGGAGT GCTCCTTTTG GCTTCCTTCC AGGCGCGGCG
10801 GCTGCTGCGC TAGCTTTTTT GGCCACTGGC CGCGCGCAGC GTAAGCGGTT AGGCTGGAAA
10861 GCGAAAGCAT TAAGTGGCTC GCTCCCTGTA GCCGGAGGGT TATTTTCCAA GGGTTGAGTC
10921 GCGGGACCCC CGGTTCGAGT CTCGGACCGG CCGGACTGCG GCGAACGGGG GTTTGCCTCC
10981 CCGTCATGCA AGACCCCGCT TGCAAATTCC TCCGGAAACA GGGACGAGCC CCTTTTTTGC
11041 TTTTCCCAGA TGCATCCGGT GCTGCGGCAG ATGCGCCCCC CTCCTCAGCA GCGGCAAGAG
11101 CAAGAGCAGC GGCAGACATG CAGGGCACCC TCCCCTCCTC CTACCGCGTC AGGAGGGGCG
11161 ACATCCGCGG TTGACGCGGC AGCAGATGGT GATTACGAAC CCCCGCGGCG CCGGGCCCGG
11221 CACTACCTGG ACTTGGAGGA GGGCGAGGGC CTGGCGCGGC TAGGAGCGCC CTCTCCTGAG
11281 CGGTACCCAA GGGTGCAGCT GAAGCGTGAT ACGCGTGAGG CGTACGTGCC GCGGCAGAAC
11341 CTGTTTCGCG ACCGCGAGGG AGAGGAGCCC GAGGAGATGC GGGATCGAAA GTTCCACGCA
11401 GGGCGCGAGC TGCGGCATGG CCTGAATCGC GAGCGGTTGC TGCGCGAGGA GGACTTTGAG
11461 CCCGACGCGC GAACCGGGAT TAGTCCCGCG CGCGCACACG TGGCGGCCGC CGACCTGGTA
11521 ACCGCATACG AGCAGACGGT GAACCAGGAG ATTAACTTTC AAAAAAGCTT TAACAACCAC
11581 GTGCGTACGC TTGTGGCGCG CGAGGAGGTG GCTATAGGAC TGATGCATCT GTGGGACTTT
11641 GTAAGCGCGC TGGAGCAAAA CCCAAATAGC AAGCCGCTCA TGGCGCAGCT GTTCCTTATA
11701 GTGCAGCACA GCAGGGACAA CGAGGCATTC AGGGATGCGC TGCTAAACAT AGTAGAGCCC
11761 GAGGGCCGCT GGCTGCTCGA TTTGATAAAC ATCCTGCAGA GCATAGTGGT GCAGGAGCGC
11821 AGCTTGAGCC TGGCTGACAA GGTGGCCGCC ATCAACTATT CCATGCTTAG CCTGGGCAAG
11881 TTTTACGCCC GCAAGATATA CCATACCCCT TACGTTCCCA TAGACAAGGA GGTAAAGATC
11941 GAGGGGTTCT ACATGCGCAT GGCGCTGAAG GTGCTTACCT TGAGCGACGA CCTGGGCGTT
12001 TATCGCAACG AGCGCATCCA CAAGGCCGTG AGCGTGAGCC GGCGGCGCGA GCTCAGCGAC
12061 CGCGAGCTGA TGCACAGCCT GCAAAGGGCC CTGGCTGGCA CGGGCAGCGG CGATAGAGAG
12121 GCCGAGTCCT ACTTTGACGC GGGCGCTGAC CTGCGCTGGG CCCCAAGCCG ACGCGCCCTG
12181 GAGGCAGCTG GGGCCGGACC TGGGCTGGCG GTGGCACCCG CGCGCGCTGG CAACGTCGGC
12241 GGCGTGGAGG AATATGACGA GGACGATGAG TACGAGCCAG AGGACGGCGA GTACTAAGCG
12301 GTGATGTTTC TGATCAGATG ATGCAAGACG CAACGGACCC GGCGGTGCGG GCGGCGCTGC
12361 AGAGCCAGCC GTCCGGCCTT AACTCCACGG ACGACTGGCG CCAGGTCATG GACCGCATCA
12421 TGTCGCTGAC TGCGCGCAAT CCTGACGCGT TCCGGCAGCA GCCGCAGGCC AACCGGCTCT
12481 CCGCAATTCT GGAAGCGGTG GTCCCGGCGC GCGCAAACCC CACGCACGAG AAGGTGCTGG
12541 CGATCGTAAA CGCGCTGGCC GAAAACAGGG CCATCCGGCC CGACGAGGCC GGCCTGGTCT
12601 ACGACGCGCT GCTTCAGCGC GTGGCTCGTT ACAACAGCGG CAACGTGCAG ACCAACCTGG
12661 ACCGGCTGGT GGGGGATGTG CGCGAGGCCG TGGCGCAGCG TGAGCGCGCG CAGCAGCAGG
12721 GCAACCTGGG CTCCATGGTT GCACTAAACG CCTTCCTGAG TACACAGCCC GCCAACGTGC
12781 CGCGGGGACA GGAGGACTAC ACCAACTTTG TGAGCGCACT GCGGCTAATG GTGACTGAGA
12841 CACCGCAAAG TGAGGTGTAC CAGTCTGGGC CAGACTATTT TTTCCAGACC AGTAGACAAG
12901 GCCTGCAGAC CGTAAACCTG AGCCAGGCTT TCAAAAACTT GCAGGGGCTG TGGGGGGTGC
12961 GGGCTCCCAC AGGCGACCGC GCGACCGTGT CTAGCTTGCT GACGCCCAAC TCGCGCCTGT
13021 TGCTGCTGCT AATAGCGCCC TTCACGGACA GTGGCAGCGT GTCCCGGGAC ACATACCTAG
13081 GTCACTTGCT GACACTGTAC CGCGAGGCCA TAGGTCAGGC GCATGTGGAC GAGCATACTT
13141 TCCAGGAGAT TACAAGTGTC AGCCGCGCGC TGGGGCAGGA GGACACGGGC AGCCTGGAGG
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FIG. 8D

13201 CAACCCTAAA CTACCTGCTG ACCAACCGGC GGCAGAAGAT CCCCTCGTTG CACAGTTTAA
13261 ACAGCGAGGA GGAGCGCATT TTGCGCTACG TGCAGCAGAG CGTGAGCCTT AACCTGATGC
13321 GCGACGGGGT AACGCCCAGC GTGGCGCTGG ACATGACCGC GCGCAACATG GAACCGGGCA
13381 TGTATGCCTC AAACCGGCCG TTTATCAACC GCCTAATGGA CTACTTGCAT CGCGCGGCCG
13441 CCGTGAACCC CGAGTATTTC ACCAATGCCA TCTTGAACCC GCACTGGCTA CCGCCCCCTG
13501 GTTTCTACAC CGGGGGATTC GAGGTGCCCG AGGGTAACGA TGGATTCCTC TGGGACGACA
13561 TAGACGACAG CGTGTTTTCC CCGCAACCGC AGACCCTGCT AGAGTTGCAA CAGCGCGAGC
13621 AGGCAGAGGC GGCGCTGCGA AAGGAAAGCT TCCGCAGGCC AAGCAGCTTG TCCGATCTAG
13681 GCGCTGCGGC CCCGCGGTCA GATGCTAGTA GCCCATTTCC AAGCTTGATA GGGTCTCTTA
13741 CCAGCACTCG CACCACCCGC CCGCGCCTGC TGGGCGAGGA GGAGTACCTA AACAACTCGC
13801 TGCTGCAGCC GCAGCGCGAA AAAAACCTGC CTCCGGCATT TCCCAACAAC GGGATAGAGA
13861 GCCTAGTGGA CAAGATGAGT AGATGGAAGA CGTACGCGCA GGAGCACAGG GACGTGCCAG
13921 GCCCGCGCCC GCCCACCCGT CGTCAAAGGC ACGACCGTCA GCGGGGTCTG GTGTGGGAGG
13981 ACGATGACTC GGCAGACGAC AGCAGCGTCC TGGATTTGGG AGGGAGTGGC AACCCGTTTG
14041 CGCACCTTCG CCCCAGGCTG GGGAGAATGT TTTAAAAAAA AAAAAGCATG ATGCAAAATA
14101 AAAAACTCAC CAAGGCCATG GCACCGAGCG TTGGTTTTCT TGTATTCCCC TTAGTATGCG
14161 GCGCGCGGCG ATGTATGAGG AAGGTCCTCC TCCCTCCTAC GAGAGTGTGG TGAGCGCGGC
14221 GCCAGTGGCG GCGGCGCTGG GTTCTCCCTT CGATGCTCCC CTGGACCCGC CGTTTGTGCC
14281 TCCGCGGTAC CTGCGGCCTA CCGGGGGGAG AAACAGCATC CGTTACTCTG AGTTGGCACC
14341 CCTATTCGAC ACCACCCGTG TGTACCTGGT GGACAACAAG TCAACGGATG TGGCATCCCT
14401 GAACTACCAG AACGACCACA GCAACTTTCT GACCACGGTC ATTCAAAACA ATGACTACAG
14461 CCCGGGGGAG GCAAGCACAC AGACCATCAA TCTTGACGAC CGGTCGCACT GGGGCGGCGA
14521 CCTGAAAACC ATCCTGCATA CCAACATGCC AAATGTGAAC GAGTTCATGT TTACCAATAA
14581 GTTTAAGGCG CGGGTGATGG TGTCGCGCTT GCCTACTAAG GACAATCAGG TGGAGCTGAA
14641 ATACGAGTGG GTGGAGTTCA CGCTGCCCGA GGGCAACTAC TCCGAGACCA TGACCATAGA
14701 CCTTATGAAC AACGCGATCG TGGAGCACTA CTTGAAAGTG GGCAGACAGA ACGGGGTTCT
14761 GGAAAGCGAC ATCGGGGTAA AGTTTGACAC CCGCAACTTC AGACTGGGGT TTGACCCCGT
14821 CACTGGTCTT GTCATGCCTG GGGTATATAC AAACGAAGCC TTCCATCCAG ACATCATTTT
14881 GCTGCCAGGA TGCGGGGTGG ACTTCACCCA CAGCCGCCTG AGCAACTTGT TGGGCATCCG
14941 CAAGCGGCAA CCCTTCCAGG AGGGCTTTAG GATCACCTAC GATGATCTGG AGGGTGGTAA
15001 CATTCCCGCA CTGTTGGATG TGGACGCCTA CCAGGCGAGC TTGAAAGATG ACACCGAACA
15061 GGGCGGGGGT GGCGCAGGCG GCAGCAACAG CAGTGGCAGC GGCGCGGAAG AGAACTCCAA
15121 CGCGGCAGCC GCGGCAATGC AGCCGGTGGA GGACATGAAC GATCATGCCA TTCGCGGCGA
15181 CACCTTTGCC ACACGGGCTG AGGAGAAGCG CGCTGAGGCC GAAGCAGCGG CCGAAGCTGC
15241 CGCCCCCGCT GCGCAACCCG AGGTCGAGAA GCCTCAGAAG AAACCGGTGA TCAAACCCCT
15301 GACAGAGGAC AGCAAGAAAC GCAGTTACAA CCTAATAAGC AATGACAGCA CCTTCACCCA
15361 GTACCGCAGC TGGTACCTTG CATACAACTA CGGCGACCCT CAGACCGGAA TCCGCTCATG
15421 GACCCTGCTT TGCACTCCTG ACGTAACCTG CGGCTCGGAG CAGGTCTACT GGTCGTTGCC
15481 AGACATGATG CAAGACCCCG TGACCTTCCG CTCCACGCGC CAGATCAGCA ACTTTCCGGT
15541 GGTGGGCGCC GAGCTGTTGC CCGTGCACTC CAAGAGCTTC TACAACGACC AGGCCGTCTA
15601 CTCCCAACTC ATCCGCCAGT TTACCTCTCT GACCCACGTG TTCAATCGCT TTCCCGAGAA
15661 CCAGATTTTG GCGCGCCCGC CAGCCCCCAC CATCACCACC GTCAGTGAAA ACGTTCCTGC
15721 TCTCACAGAT CACGGGACGC TACCGCTGCG CAACAGCATC GGAGGAGTCC AGCGAGTGAC
15781 CATTACTGAC GCCAGACGCC GCACCTGCCC CTACGTTTAC AAGGCCCTGG GCATAGTCTC
15841 GCCGCGCGTC CTATCGAGCC GCACTTTTTG AGCAAGCATG TCCATCCTTA TATCGCCCAG
15901 CAATAACACA GGCTGGGGCC TGCGCTTCCC AAGCAAGATG TTTGGCGGGG CCAAGAAGCG
15961 CTCCGACCAA CACCCAGTGC GCGTGCGCGG GCACTACCGC GCGCCCTGGG GCGCGCACAA
16021 ACGCGGCCGC ACTGGGCGCA CCACCGTCGA TGACGCCATC GACGCGGTGG TGGAGGAGGC
16081 GCGCAACTAC ACGCCCACGC CGCCACCAGT GTCCACAGTG GACGCGGCCA TTCAGACCGT
16141 GGTGCGCGGA GCCCGGCGCT ATGCTAAAAT GAAGAGACGG CGGAGGCGCG TAGCACGTCG
16201 CCACCGCCGC CGACCCGGCA CTGCCGCCCA ACGCGCGGCG GCGGCCCTGC TTAACCGCGC
16261 ACGTCGCACC GGCCGACGGG CGGCCATGCG GGCCGCTCGA AGGCTGGCCG CGGGTATTGT
16321 CACTGTGCCC CCCAGGTCCA GGCGACGAGC GGCCGCCGCA GCAGCCGCGG CCATTAGTGC
16381 TATGACTCAG GGTCGCAGGG GCAACGTGTA TTGGGTGCGC GACTCGGTTA GCGGCCTGCG
16441 CGTGCCCGTG CGCACCCGCC CCCCGCGCAA CTAGATTGCA AGAAAAAACT ACTTAGACTC

FIG. 8E

16501 GTACTGTTGT ATGTATCCAG CGGCGGCGGC GCGCAACGAA GCTATGTCCA AGCGCAAAAT
16561 CAAAGAAGAG ATGCTCCAGG TCATCGCGCC GGAGATCTAT GGCCCCCCGA AGAAGGAAGA
16621 GCAGGATTAC AAGCCCCGAA AGCTAAAGCG GGTCAAAAAG AAAAAGAAAG ATGATGATGA
16681 TGAACTTGAC GACGAGGTGG AACTGCTGCA CGCTACCGCG CCCAGGCGAC GGGTACAGTG
16741 GAAAGGTCGA CGCGTAAAAC GTGTTTTGCG ACCCGGCACC ACCGTAGTCT TTACGCCCGG
16801 TGAGCGCTCC ACCCGCACCT ACAAGCGCGT GTATGATGAG GTGTACGGCG ACGAGGACCT
16861 GCTTGAGCAG GCCAACGAGC GCCTCGGGGA GTTTGCCTAC GGAAAGCGGC ATAAGGACAT
16921 GCTGGCGTTG CCGCTGGACG AGGGCAACCC AACACCTAGC CTAAAGCCCG TAACACTGCA
16981 GCAGGTGCTG CCCGCGCTTG CACCGTCCGA AGAAAAGCGC GGCCTAAAGC GCGAGTCTGG
17041 TGACTTGGCA CCCACCGTGC AGCTGATGGT ACCCAAGCGC CAGCGACTGG AAGATGTCTT
17101 GGAAAAAATG ACCGTGGAAC CTGGGCTGGA GCCCGAGGTC CGCGTGCGGC CAATCAAGCA
17161 GGTGGCGCCG GGACTGGGCG TGCAGACCGT GGACGTTCAG ATACCCACTA CCAGTAGCAC
17221 CAGTATTGCC ACCGCCACAG AGGGCATGGA GACACAAACG TCCCCGGTTG CCTCAGCGGT
17281 GGCGGATGCC GCGGTGCAGG CGGTCGCTGC GGCCGCGTCC AAGACCTCTA CGGAGGTGCA
17341 AACGGACCCG TGGATGTTTC GCGTTTCAGC CCCCCGGCGC CCGCGCGGTT CGAGGAAGTA
17401 CGGCGCCGCC AGCGCGCTAC TGCCCGAATA TGCCCTACAT CCTTCCATTG CGCCTACCCC
17461 CGGCTATCGT GGCTACACCT ACCGCCCCAG AAGACGAGCA ACTACCCGAC GCCGAACCAC
17521 CACTGGAACC CGCCGCCGCC GTCGCCGTCG CCAGCCCGTG CTGGCCCCGA TTTCCGTGCG
17581 CAGGGTGGCT CGCGAAGGAG GCAGGACCCT GGTGCTGCCA ACAGCGCGCT ACCACCCCAG
17641 CATCGTTTAA AAGCCGGTCT TTGTGGTTCT TGCAGATATG GCCCTCACCT GCCGCCTCCG
17701 TTTCCCGGTG CCGGGATTCC GAGGAAGAAT GCACCGTAGG AGGGGCATGG CCGGCCACGG
17761 CCTGACGGGC GGCATGCGTC GTGCGCACCA CCGGCGGCGG CGCGCGTCGC ACCGTCGCAT
17821 GCGCGGCGGT ATCCTGCCCC TCCTTATTCC ACTGATCGCC GCGGCGATTG GCGCCGTGCC
17881 CGGAATTGCA TCCGTGGCCT TGCAGGCGCA GAGACACTGA TTAAAAACAA GTTGCATGTG
17941 GAAAAATCAA AATAAAAAGT CTGGACTCTC ACGCTCGCTT GGTCCTGTAA CTATTTTGTA
18001 GAATGGAAGA CATCAACTTT GCGTCTCTGG CCCCGCGACA CGGCTCGCGC CCGTTCATGG
18061 GAAACTGGCA AGATATCGGC ACCAGCAATA TGAGCGGTGG CGCCTTCAGC TGGGGCTCGC
18121 TGTGGAGCGG CATTAAAAAT TTCGGTTCCA CCGTTAAGAA CTATGGCAGC AAGGCCTGGA
18181 ACAGCAGCAC AGGCCAGATG CTGAGGGATA AGTTGAAAGA GCAAAATTTC CAACAAAAGG
18241 TGGTAGATGG CCTGGCCTCT GGCATTAGCG GGGTGGTGGA CCTGGCCAAC CAGGCAGTGC
18301 AAAATAAGAT TAACAGTAAG CTTGATCCCC GCCCTCCCGT AGAGGAGCCT CCACCGGCCG
18361 TGGAGACAGT GTCTCCAGAG GGGCGTGGCG AAAAGCGTCC GCGCCCCGAC AGGGAAGAAA
18421 CTCTGGTGAC GCAAATAGAC GAGCCTCCCT CGTACGAGGA GGCACTAAAG CAAGGCCTGC
18481 CCACCACCCG TCCCATCGCG CCCATGGCTA CCGGAGTGCT GGGCCAGCAC ACACCCGTAA
18541 CGCTGGACCT GCCTCCCCCC GCCGACACCC AGCAGAAACC TGTGCTGCCA GGCCCGACCG
18601 CCGTTGTTGT AACCCGTCCT AGCCGCGCGT CCCTGCGCCG CGCCGCCAGC GGTCCGCGAT
18661 CGTTGCGGCC CGTAGCCAGT GGCAACTGGC AAAGCACACT GAACAGCATC GTGGGTCTGG
18721 GGGTGCAATC CCTGAAGCGC CGACGATGCT TCTGAATAGC TAACGTGTCG TATGTGTGTC
18781 ATGTATGCGT CCATGTCGCC GCCAGAGGAG CTGCTGAGCC GCCGCGCGCC CGCTTTCCAA
18841 GATGGCTACC CCTTCGATGA TGCCGCAGTG GTCTTACATG CACATCTCGG GCCAGGACGC
18901 CTCGGAGTAC CTGAGCCCCG GGCTGGTGCA GTTTGCCCGC GCCACCGAGA CGTACTTCAG
18961 CCTGAATAAC AAGTTTAGAA ACCCCACGGT GGCGCCTACG CACGACGTGA CCACAGACCG
19021 GTCCCAGCGT TTGACGCTGC GGTTCATCCC TGTGGACCGT GAGGATACTG CGTACTCGTA
19081 CAAGGCGCGG TTCACCCTAG CTGTGGGTGA TAACCGTGTG CTGGACATGG CTTCCACGTA
19141 CTTTGACATC CGCGGCGTGC TGGACAGGGG CCCTACTTTT AAGCCCTACT CTGGCACTGC
19201 CTACAACGCC CTGGCTCCCA AGGGTGCCCC AAATCCTTGC GAATGGGATG AAGCTGCTAC
19261 TGCTCTTGAA ATAAACCTAG AAGAAGAGGA CGATGACAAC GAAGACGAAG TAGACGAGCA
19321 AGCTGAGCAG CAAAAAACTC ACGTATTTGG GCAGGCGCCT TATTCTGGTA TAAATATTAC
19381 AAAGGAGGGT ATTCAAATAG GTGTCGAAGG TCAAACACCT AAATATGCCG ATAAAACATT
19441 TCAACCTGAA CCTCAAATAG GAGAATCTCA GTGGTACGAA ACTGAAATTA ATCATGCAGC
19501 TGGGAGAGTC CTTAAAAAGA CTACCCCAAT GAAACCATGT TACGGTTCAT ATGCAAAACC
19561 CACAAATGAA AATGGAGGGC AAGGCATTCT TGTAAAGCAA CAAAATGGAA AGCTAGAAAG
19621 TCAAGTGGAA ATGCAATTTT TCTCAACTAC TGAGGCGACC GCAGGCAATG GTGATAACTT
19681 GACTCCTAAA GTGGTATTGT ACAGTGAAGA TGTAGATATA GAAACCCCAG ACACTCATAT
19741 TTCTTACATG CCCACTATTA AGGAAGGTAA CTCACGAGAA CTAATGGGCC AACAATCTAT

FIG. 8F

19801 GCCCAACAGG CCTAATTACA TTGCTTTTAG GGACAATTTT ATTGGTCTAA TGTATTACAA
19861 CAGCACGGGT AATATGGGTG TTCTGGCGGG CCAAGCATCG CAGTTGAATG CTGTTGTAGA
19921 TTTGCAAGAC AGAAACACAG AGCTTTCATA CCAGCTTTTG CTTGATTCCA TTGGTGATAG
19981 AACCAGGTAC TTTTCTATGT GGAATCAGGC TGTTGACAGC TATGATCCAG ATGTTAGAAT
20041 TATTGAAAAT CATGGAACTG AAGATGAACT TCCAAATTAC TGCTTTCCAC TGGGAGGTGT
20101 GATTAATACA GAGACTCTTA CCAAGGTAAA ACCTAAAACA GGTCAGGAAA ATGGATGGGA
20161 AAAAGATGCT ACAGAATTTT CAGATAAAAA TGAAATAAGA GTTGGAAATA ATTTTGCCAT
20221 GGAAATCAAT CTAAATGCCA ACCTGTGGAG AAATTTCCTG TACTCCAACA TAGCGCTGTA
20281 TTTGCCCGAC AAGCTAAAGT ACAGTCCTTC CAACGTAAAA ATTTCTGATA ACCCAAACAC
20341 CTACGACTAC ATGAACAAGC GAGTGGTGGC TCCCGGGTTA GTGGACTGCT ACATTAACCT
20401 TGGAGCACGC TGGTCCCTTG ACTATATGGA CAACGTCAAC CCATTTAACC ACCACCGCAA
20461 TGCTGGCCTG CGCTACCGCT CAATGTTGCT GGGCAATGGT CGCTATGTGC CCTTCCACAT
20521 CCAGGTGCCT CAGAAGTTCT TTGCCATTAA AAACCTCCTT CTCCTGCCGG GCTCATACAC
20581 CTACGAGTGG AACTTCAGGA AGGATGTTAA CATGGTTCTG CAGAGCTCCC TAGGAAATGA
20641 CCTAAGGGTT GACGGAGCCA GCATTAAGTT TGATAGCATT TGCCTTTACG CCACCTTCTT
20701 CCCCATGGCC CACAACACCG CCTCCACGCT TGAGGCCATG CTTAGAAACG ACACCAACGA
20761 CCAGTCCTTT AACGACTATC TCTCCGCCGC CAACATGCTC TACCCTATAC CCGCCAACGC
20821 TACCAACGTG CCCATATCCA TCCCCTCCCG CAACTGGGCG GCTTTCCGCG GCTGGGCCTT
20881 CACGCGCCTT AAGACTAAGG AAACCCCATC ACTGGGCTCG GGCTACGACC CTTATTACAC
20941 CTACTCTGGC TCTATACCCT ACCTAGATGG AACCTTTTAC CTCAACCACA CCTTTAAGAA
21001 GGTGGCCATT ACCTTTGACT CTTCTGTCAG CTGGCCTGGC AATGACCGCC TGCTTACCCC
21061 CAACGAGTTT GAAATTAAGC GCTCAGTTGA CGGGGAGGGT TACAACGTTG CCCAGTGTAA
21121 CATGACCAAA GACTGGTTCC TGGTACAAAT GCTAGCTAAC TACAACATTG GCTACCAGGG
21181 CTTCTATATC CCAGAGAGCT ACAAGGACCG CATGTACTCC TTCTTTAGAA ACTTCCAGCC
21241 CATGAGCCGT CAGGTGGTGG ATGATACTAA ATACAAGGAC TACCAACAGG TGGGCATCCT
21301 ACACCAACAC AACAACTCTG GATTTGTTGG CTACCTTGCC CCCACCATGC GCGAAGGACA
21361 GGCCTACCCT GCTAACTTCC CCTATCCGCT TATAGGCAAG ACCGCAGTTG ACAGCATTAC
21421 CCAGAAAAAG TTTCTTTGCG ATCGCACCCT TTGGCGCATC CCATTCTCCA GTAACTTTAT
21481 GTCCATGGGC GCACTCACAG ACCTGGGCCA AAACCTTCTC TACGCCAACT CCGCCCACGC
21541 GCTAGACATG ACTTTTGAGG TGGATCCCAT GGACGAGCCC ACCCTTCTTT ATGTTTTGTT
21601 TGAAGTCTTT GACGTGGTCC GTGTGCACCG GCCGCACCGC GGCGTCATCG AAACCGTGTA
21661 CCTGCGCACG CCCTTCTCGG CCGGCAACGC CACAACATAA AGAAGCAAGC AACATCAACA
21721 ACAGCTGCCG CCATGGGCTC CAGTGAGCAG GAACTGAAAG CCATTGTCAA AGATCTTGGT
21781 TGTGGGCCAT ATTTTTTGGG CACCTATGAC AAGCGCTTTC CAGGCTTTGT TTCTCCACAC
21841 AAGCTCGCCT GCGCCATAGT CAATACGGCC GGTCGCGAGA CTGGGGGCGT ACACTGGATG
21901 GCCTTTGCCT GGAACCCGCA CTCAAAAACA TGCTACCTCT TTGAGCCCTT TGGCTTTTCT
21961 GACCAGCGAC TCAAGCAGGT TTACCAGTTT GAGTACGAGT CACTCCTGCG CCGTAGCGCC
22021 ATTGCTTCTT CCCCCGACCG CTGTATAACG CTGGAAAAGT CCACCCAAAG CGTACAGGGG
22081 CCCAACTCGG CCGCCTGTGG ACTATTCTGC TGCATGTTTC TCCACGCCTT TGCCAACTGG
22141 CCCCAAACTC CCATGGATCA CAACCCCACC ATGAACCTTA TTACCGGGGT ACCCAACTCC
22201 ATGCTCAACA GTCCCCAGGT ACAGCCCACC CTGCGTCGCA ACCAGGAACA GCTCTACAGC
22261 TTCCTGGAGC GCCACTCGCC CTACTTCCGC AGCCACAGTG CGCAGATTAG GAGCGCCACT
22321 TCTTTTTGTC ACTTGAAAAA CATGTAAAAA TAATGTACTA GAGACACTTT CAATAAAGGC
22381 AAATGCTTTT ATTTGTACAC TCTCGGGTGA TTATTTACCC CCACCCTTGC CGTCTGCGCC
22441 GTTTAAAAAT CAAAGGGGTT CTGCCGCGCA TCGCTATGCG CCACTGGCAG GGACACGTTG
22501 CGATACTGGT GTTTAGTGCT CCACTTAAAC TCAGGCACAA CCATCCGCGG CAGCTCGGTG
22561 AAGTTTTCAC TCCACAGGCT GCGCACCATC ACCAACGCGT TTAGCAGGTC GGGCGCCGAT
22621 ATCTTGAAGT CGCAGTTGGG GCCTCCGCCC TGCGCGCGCG AGTTGCGATA CACAGGGTTG
22681 CAGCACTGGA ACACTATCAG CGCCGGGTGG TGCACGCTGG CCAGCACGCT CTTGTCGGAG
22741 ATCAGATCCG CGTCCAGGTC CTCCGCGTTG CTCAGGGCGA ACGGAGTCAA CTTTGGTAGC
22801 TGCCTTCCCA AAAAGGGCGC GTGCCCAGGC TTTGAGTTGC ACTCGCACCG TAGTGGCATC
22861 AAAAGGTGAC CGTGCCCGGT CTGGGCGTTA GGATACAGCG CCTGCATAAA AGCCTTGATC
22921 TGCTTAAAAG CCACCTGAGC CTTTGCGCCT TCAGAGAAGA ACATGCCGCA AGACTTGCCG
22981 GAAAACTGAT TGGCCGGACA GGCCGCGTCG TGCACGCAGC ACCTTGCGTC GGTGTTGGAG
23041 ATCTGCACCA CATTTCGGCC CCACCGGTTC TTCACGATCT TGGCCTTGCT AGACTGCTCC

FIG. 8G

23101 TTCAGCGCGC GCTGCCCGTT TTCGCTCGTC ACATCCATTT CAATCACGTG CTCCTTATTT
23161 ATCATAATGC TTCCGTGTAG ACACTTAAGC TCGCCTTCGA TCTCAGCGCA GCGGTGCAGC
23221 CACAACGCGC AGCCCGTGGG CTCGTGATGC TTGTAGGTCA CCTCTGCAAA CGACTGCAGG
23281 TACGCCTGCA GGAATCGCCC CATCATCGTC ACAAAGGTCT TGTTGCTGGT GAAGGTCAGC
23341 TGCAACCCGC GGTGCTCCTC GTTCAGCCAG GTCTTGCATA CGGCCGCCAG AGCTTCCACT
23401 TGGTCAGGCA GTAGTTTGAA GTTCGCCTTT AGATCGTTAT CCACGTGGTA CTTGTCCATC
23461 AGCGCGCGCG CAGCCTCCAT GCCCTTCTCC CACGCAGACA CGATCGGCAC ACTCAGCGGG
23521 TTCATCACCG TAATTTCACT TTCCGCTTCG CTGGGCTCTT CCTCTTCCTC TTGCGTCCGC
23581 ATACCACGCG CCACTGGGTC GTCTTCATTC AGCCGCCGCA CTGTGCGCTT ACCTCCTTTG
23641 CCATGCTTGA TTAGCACCGG TGGGTTGCTG AAACCCACCA TTTGTAGCGC CACATCTTCT
23701 CTTTCTTCCT CGCTGTCCAC GATTACCTCT GGTGATGGCG GGCGCTCGGG CTTGGGAGAA
23761 GGGCGCTTCT TTTTCTTCTT GGGCGCAATG GCCAAATCCG CCGCCGAGGT CGATGGCCGC
23821 GGGCTGGGTG TGCGCGGCAC CAGCGCGTCT TGTGATGAGT CTTCCTCGTC CTCGGACTCG
23881 ATACGCCGCC TCATCCGCTT TTTTGGGGGC GCCCGGGGAG GCGGCGGCGA CGGGGACGGG
23941 GACGACACGT CCTCCATGGT TGGGGGACGT CGCGCCGCAC CGCGTCCGCG CTCGGGGGTG
24001 GTTTCGCGCT GCTCCTCTTC CCGACTGGCC ATTTCCTTCT CCTATAGGCA GAAAAAGATC
24061 ATGGAGTCAG TCGAGAAGAA GGACAGCCTA ACCGCCCCCT CTGAGTTCGC CACCACCGCC
24121 TCCACCGATG CCGCCAACGC GCCTACCACC TTCCCCGTCG AGGCACCCCC GCTTGAGGAG
24181 GAGGAAGTGA TTATCGAGCA GGACCCAGGT TTTGTAAGCG AAGACGACGA GGACCGCTCA
24241 GTACCAACAG AGGATAAAAA GCAAGACCAG GACAACGCAG AGGCAAACGA GGAACAAGTC
24301 GGGCGGGGGG ACGAAAGGCA TGGCGACTAC CTAGATGTGG GAGACGACGT GCTGTTGAAG
24361 CATCTGCAGC GCCAGTGCGC CATTATCTGC GACGCGTTGC AAGAGCGCAG CGATGTGCCC
24421 CTCGCCATAG CGGATGTCAG CCTTGCCTAC GAACGCCACC TATTCTCACC GCGCGTACCC
24481 CCCAAACGCC AAGAAAACGG CACATGCGAG CCCAACCCGC GCCTCAACTT CTACCCCGTA
24541 TTTGCCGTGC CAGAGGTGCT TGCCACCTAT CACATCTTTT TCCAAAACTG CAAGATACCC
24601 CTATCCTGCC GTGCCAACCG CAGCCGAGCG GACAAGCAGC TGGCCTTGCG GCAGGGCGCT
24661 GTCATACCTG ATATCGCCTC GCTCAACGAA GTGCCAAAAA TCTTTGAGGG TCTTGGACGC
24721 GACGAGAAGC GCGCGGCAAA CGCTCTGCAA CAGGAAAACA GCGAAAATGA AAGTCACTCT
24781 GGAGTGTTGG TGGAACTCGA GGGTGACAAC GCGCGCCTAG CCGTACTAAA ACGCAGCATC
24841 GAGGTCACCC ACTTTGCCTA CCCGGCACTT AACCTACCCC CCAAGGTCAT GAGCACAGTC
24901 ATGAGTGAGC TGATCGTGCG CCGTGCGCAG CCCCTGGAGA GGGATGCAAA TTTGCAAGAA
24961 CAAACAGAGG AGGGCCTACC CGCAGTTGGC GACGAGCAGC TAGCGCGCTG GCTTCAAACG
25021 CGCGAGCCTG CCGACTTGGA GGAGCGACGC AAACTAATGA TGGCCGCAGT GCTCGTTACC
25081 GTGGAGCTTG AGTGCATGCA GCGGTTCTTT GCTGACCCGG AGATGCAGCG CAAGCTAGAG
25141 GAAACATTGC ACTACACCTT TCGACAGGGC TACGTACGCC AGGCCTGCAA GATCTCCAAC
25201 GTGGAGCTCT GCAACCTGGT CTCCTACCTT GGAATTTTGC ACGAAAACCG CCTTGGGCAA
25261 AACGTGCTTC ATTCCACGCT CAAGGGCGAG GCGCGCCGCG ACTACGTCCG CGACTGCGTT
25321 TACTTATTTC TATGCTACAC CTGGCAGACG GCCATGGGCG TTTGGCAGCA GTGCTTGGAG
25381 GAGTGCAACC TCAAGGAGCT GCAGAAACTG CTAAAGCAAA ACTTGAAGGA CCTATGGACG
25441 GCCTTCAACG AGCGCTCCGT GGCCGCGCAC CTGGCGGACA TCATTTTCCC CGAACGCCTG
25501 CTTAAAACCC TGCAACAGGG TCTGCCAGAC TTCACCAGTC AAAGCATGTT GCAGAACTTT
25561 AGGAACTTTA TCCTAGAGCG CTCAGGAATC TTGCCCGCCA CCTGCTGTGC ACTTCCTAGC
25621 GACTTTGTGC CCATTAAGTA CCGCGAATGC CCTCCGCCGC TTTGGGGCCA CTGCTACCTT
25681 CTGCAGCTAG CCAACTACCT TGCCTACCAC TCTGACATAA TGGAAGACGT GAGCGGTGAC
25741 GGTCTACTGG AGTGTCACTG TCGCTGCAAC CTATGCACCC CGCACCGCTC CCTGGTTTGC
25801 AATTCGCAGC TGCTTAACGA AAGTCAAATT ATCGGTACCT TTGAGCTGCA GGGTCCCTCG
25861 CCTGACGAAA AGTCCGCGGC TCCGGGGTTG AAACTCACTC CGGGGCTGTG GACGTCGGCT
25921 TACCTTCGCA AATTTGTACC TGAGGACTAC CACGCCCACG AGATTAGGTT CTACGAAGAC
25981 CAATCCCGCC CGCCAAATGC GGAGCTTACC GCCTGCGTCA TTACCCAGGG CCACATTCTT
26041 GGCCAATTGC AAGCCATCAA CAAAGCCCGC CAAGAGTTTC TGCTACGAAA GGGACGGGGG
26101 GTTTACTTGG ACCCCCAGTC CGGCGAGGAG CTCAACCCAA TCCCCCCGCC GCCGCAGCCC
26161 TATCAGCAGC AGCCGCGGGC CCTTGCTTCC CAGGATGGCA CCCAAAAAGA AGCTGCAGCT
26221 GCCGCCGCCA CCCACGGACG AGGAGGAATA CTGGGACAGT CAGGCAGAGG AGGTTTTGGA
26281 CGAGGAGGAG GAGGACATGA TGGAAGACTG GGAGAGCCTA GACGAGGAAG CTTCCGAGGT
26341 CGAAGAGGTG TCAGACGAAA CACCGTCACC CTCGGTCGCA TTCCCCTCGC CGGCGCCCCA

FIG. 8H

26401	GAAATCGGCA	ACCGGTTCCA	GCATGGCTAC	AACCTCCGCT	CCTCAGGCGC	CGCCGGCACT
26461	GCCCGTTCGC	CGACCCAACC	GTAGATGGGA	CACCACTGGA	ACCAGGGCCG	GTAAGTCCAA
26521	GCAGCCGCCG	CCGTTAGCCC	AAGAGCAACA	ACAGCGCCAA	GGCTACCGCT	CATGGCGCGG
26581	GCACAAGAAC	GCCATAGTTG	CTTGCTTGCA	AGACTGTGGG	GGCAACATCT	CCTTCGCCCG
26641	CCGCTTTCTT	CTCTACCATC	ACGGCGTGGC	CTTCCCCCGT	AACATCCTGC	ATTACTACCG
26701	TCATCTCTAC	AGCCCATACT	GCACCGGCGG	CAGCGGCAGC	GGCAGCAACA	GCAGCGGCCA
26761	CACAGAAGCA	AAGGCGACCG	GATAGCAAGA	CTCTGACAAA	GCCCAAGAAA	TCCACAGCGG
26821	CGGCAGCAGC	AGGAGGAGGA	GCGCTGCGTC	TGGCGCCCAA	CGAACCCGTA	TCGACCCGCG
26881	AGCTTAGAAA	CAGGATTTTT	CCCACTCTGT	ATGCTATATT	TCAACAGAGC	AGGGGCCAAG
26941	AACAAGAGCT	GAAAATAAAA	AACAGGTCTC	TGCGATCCCT	CACCCGCAGC	TGCCTGTATC
27001	ACAAAAGCGA	AGATCAGCTT	CGGCGCACGC	TGGAAGACGC	GGAGGCTCTC	TTCAGTAAAT
27061	ACTGCGCGCT	GACTCTTAAG	GACTAGTTTC	GCGCCCTTTC	TCAAATTTAA	GCGCGAAAAC
27121	TACGTCATCT	CCAGCGGCCA	CACCCGGCGC	CAGCACCTGT	CGTCAGCGCC	ATTATGAGCA
27181	AGGAAATTCC	CACGCCCTAC	ATGTGGAGTT	ACCAGCCACA	AATGGGACTT	GCGGCTGGAG
27241	CTGCCCAAGA	CTACTCAACC	CGAATAAACT	ACATGAGCGC	GGGACCCCAC	ATGATATCCC
27301	GGGTCAACGG	AATCCGCGCC	CACCGAAACC	GAATTCTCTT	GGAACAGGCG	GCTATTACCA
27361	CCACACCTCG	TAATAACCTT	AATCCCCGTA	GTTGGCCCGC	TGCCCTGGTG	TACCAGGAAA
27421	GTCCCGCTCC	CACCACTGTG	GTACTTCCCA	GAGACGCCCA	GGCCGAAGTT	CAGATGACTA
27481	ACTCAGGGGC	GCAGCTTGCG	GGCGGCTTTC	GTCACAGGGT	GCGGTCGCCC	GGGCAGGGTA
27541	TAACTCACCT	GACAATCAGA	GGGCGAGGTA	TTCAGCTCAA	CGACGAGTCG	GTGAGCTCCT
27601	CGCTTGGTCT	CCGTCCGGAC	GGGACATTTC	AGATCGGCGG	CGCCGGCCGT	CCTTCATTCA
27661	CGCCTCGTCA	GGCAATCCTA	ACTCTGCAGA	CCTCGTCCTC	TGAGCCGCGC	TCTGGAGGCA
27721	TTGGAACTCT	GCAATTTATT	GAGGAGTTTG	TGCCATCGGT	CTACTTTAAC	CCCTTCTCGG
27781	GACCTCCCGG	CCACTATCCG	GATCAATTTA	TTCCTAACTT	TGACGCGGTA	AAGGACTCGG
27841	CGGACGGCTA	CGACTGAATG	TTAAGTGGAG	AGGCAGAGCA	ACTGCGCCTG	AAACACCTGG
27901	TCCACTGTCG	CCGCCACAAG	TGCTTTGCCC	GCGACTCCGG	TGAGTTTTGC	TACTTTGAAT
27961	TGCCCGAGGA	TCATATCGAG	GGCCCGGCGC	ACGGCGTCCG	GCTTACCGCC	CAGGGAGAGC
28021	TTGCCCGTAG	CCTGATTCGG	GAGTTTACCC	AGCGCCCCCT	GCTAGTTGAG	CGGGACAGGG
28081	GACCCTGTGT	TCTCACTGTG	ATTTGCAACT	GTCCTAACCT	TGGATTACAT	CAAGATCTTT
28141	GTTGCCATCT	CTGTGCTGAG	TATAATAAAT	ACAGAAATTA	AAATATACTG	GGGCTCCTAT
28201	CGCCATCCTG	TAAACGCCAC	CGTCTTCACC	CGCCCAAGCA	AACCAAGGCG	AACCTTACCT
28261	GGTACTTTTA	ACATCTCTCC	CTCTGTGATT	TACAACAGTT	TCAACCCAGA	CGGAGTGAGT
28321	CTACGAGAGA	ACCTCTCCGA	GCTCAGCTAC	TCCATCAGAA	AAAACACCAC	CCTCCTTACC
28381	TGCCGGGAAC	GTACGAGTGC	GTCACCGGCC	GCTGCACCAC	ACCTACCGCC	TGACCGTAAA
28441	CCAGACTTTT	TCCGGACAGA	CCTCAATAAC	TCTGTTTACC	AGAACAGGAG	GTGAGCTTAG
28501	AAAACCCTTA	GGGTATTAGG	CCAAAGGCGC	AGCTACTGTG	GGGTTTATGA	ACAATTCAAG
28561	CAACTCTACG	GGCTATTCTA	ATTCAGGTTT	CTCTAGAATC	GGGGTTGGGG	TTATTCTCTG
28621	TCTTGTGATT	CTCTTTATTC	TTATACTAAC	GCTTCTCTGC	CTAAGGCTCG	CCGCCTGCTG
28681	TGTGCACATT	TGCATTTATT	GTCAGCTTTT	TAAACGCTGG	GGTCGCCACC	CAAGATGATT
28741	AGGTACATAA	TCCTAGGTTT	ACTCACCCTT	GCGTCAGCCC	ACGGTACCAC	CCAAAAGGTG
28801	GATTTTAAGG	AGCCAGCCTG	TAATGTTACA	TTCGCAGCTG	AAGCTAATGA	GTGCACCACT
28861	CTTATAAAAT	GCACCACAGA	ACATGAAAAG	CTGCTTATTC	GCCACAAAAA	CAAAATTGGC
28921	AAGTATGCTG	TTTATGCTAT	TTGGCAGCCA	GGTGACACTA	CAGAGTATAA	TGTTACAGTT
28981	TTCCAGGGTA	AAAGTCATAA	AACTTTTATG	TATACTTTTC	CATTTTATGA	AATGTGCGAC
29041	ATTACCATGT	ACATGAGCAA	ACAGTATAAG	TTGTGGCCCC	CACAAAATTG	TGTGGAAAAC
29101	ACTGGCACTT	TCTGCTGCAC	TGCTATGCTA	ATTACAGTGC	TCGCTTTGGT	CTGTACCCTA
29161	CTCTATATTA	AATACAAAAG	CAGACGCAGC	TTTATTGAGG	AAAAGAAAAT	GCCTTAATTT
29221	ACTAAGTTAC	AAAGCTAATG	TCACCACTAA	CTGCTTTACT	CGCTGCTTGC	AAAACAAATT
29281	CAAAAAGTTA	GCATTATAAT	TAGAATAGGA	TTTAAACCCC	CCGGTCATTT	CCTGCTCAAT
29341	ACCATTCCCC	TGAACAATTG	ACTCTATGTG	GGATATGCTC	CAGCGCTACA	ACCTTGAAGT
29401	CAGGCTTCCT	GGATGTCAGC	ATCTGACTTT	GGCCAGCACC	TGTCCCGCGG	ATTTGTTCCA
29461	GTCCAACTAC	AGCGACCCAC	CCTAACAGAG	ATGACCAACA	CAACCAACGC	GGCCGCCGCT
29521	ACCGGACTTA	CATCTACCAC	AAATACACCC	CAAGTTTCTG	CCTTTGTCAA	TAACTGGGAT
29581	AACTTGGGCA	TGTGGTGGTT	CTCCATAGCG	CTTATGTTTG	TATGCCTTAT	TATTATGTGG
29641	CTCATCTGCT	GCCTAAAGCG	CAAACGCGCC	CGACCACCCA	TCTATAGTCC	CATCATTGTG

FIG. 8I

29701 CTACACCCAA ACAATGATGG AATCCATAGA TTGGACGGAC TGAAACACAT GTTCTTTTCT
29761 CTTACAGTAT GATTAAATGA GACATGATTC CTCGAGTTTT TATATTACTG ACCCTTGTTG
29821 CGCTTTTTTG TGCGTGCTCC ACATTGGCTG CGGTTTCTCA CATCGAAGTA GACTGCATTC
29881 CAGCCTTCAC AGTCTATTTG CTTTACGGAT TTGTCACCCT CACGCTCATC TGCAGCCTCA
29941 TCACTGTGGT CATCGCCTTT ATCCAGTGCA TTGACTGGGT CTGTGTGCGC TTTGCATATC
30001 TCAGACACCA TCCCCAGTAC AGGGACAGGA CTATAGCTGA GCTTCTTAGA ATTCTTTAAT
30061 TATGAAATTT ACTGTGACTT TTCTGCTGAT TATTTGCACC CTATCTGCGT TTTGTTCCCC
30121 GACCTCCAAG CCTCAAAGAC ATATATCATG CAGATTCACT CGTATATGGA ATATTCCAAG
30181 TTGCTACAAT GAAAAAAGCG ATCTTTCCGA AGCCTGGTTA TATGCAATCA TCTCTGTTAT
30241 GGTGTTCTGC AGTACCATCT TAGCCCTAGC TATATATCCC TACCTTGACA TTGGCTGGAA
30301 ACGAATAGAT GCCATGAACC ACCCAACTTT CCCCGCGCCC GCTATGCTTC CACTGCAACA
30361 AGTTGTTGCC GGCGGCTTTG TCCCAGCCAA TCAGCCTCGC CCCACTTCTC CCACCCCCAC
30421 TGAAATCAGC TACTTTAATC TAACAGGAGG AGATGACTGA CACCCTAGAT CTAGAAATGG
30481 ACGGAATTAT TACAGAGCAG CGCCTGCTAG AAAGACGCAG GGCAGCGGCC GAGCAACAGC
30541 GCATGAATCA AGAGCTCCAA GACATGGTTA ACTTGCACCA GTGCAAAAGG GGTATCTTTT
30601 GTCTGGTAAA GCAGGCCAAA GTCACCTACG ACAGTAATAC CACCGGACAC CGCCTTAGCT
30661 ACAAGTTGCC AACCAAGCGT CAGAAATTGG TGGTCATGGT GGGAGAAAAG CCCATTACCA
30721 TAACTCAGCA CTCGGTAGAA ACCGAAGGCT GCATTCACTC ACCTTGTCAA GGACCTGAGG
30781 ATCTCTGCAC CCTTATTAAG ACCCTGTGCG GTCTCAAAGA TCTTATTCCC TTTAACTAAT
30841 AAAAAAAAAT AATAAAGCAT CACTTACTTA AAATCAGTTA GCAAATTTCT GTCCAGTTTA
30901 TTCAGCAGCA CCTCCTTGCC CTCCTCCCAG CTCTGGTATT GCAGCTTCCT CCTGGCTGCA
30961 AACTTTCTCC ACAATCTAAA TGGAATGTCA GTTTCCTCCT GTTCCTGTCC ATCCGCACCC
31021 ACTATCTTCA TGTTGTTGCA GATGAAGCGC GCAAGACCGT CTGAAGATAC CTTCAACCCC
31081 GTGTATCCAT ATGACACGGA AACCGGTCCT CCAACTGTGC CTTTTCTTAC TCCTCCCTTT
31141 GTATCCCCCA ATGGGTTTCA AGAGAGTCCC CCTGGGGTAC TCTCTTTGCG CCTATCCGAA
31201 CCTCTAGTTA CCTCCAATGG CATGCTTGCG CTCAAAATGG GCAACGGCCT CTCTCTGGAC
31261 GAGGCCGGCA ACCTTACCTC CCAAAATGTA ACCACTGTGA GCCCACCTCT CAAAAAAACC
31321 AAGTCAAACA TAAACCTGGA AATATCTGCA CCCCTCACAG TTACCTCAGA AGCCCTAACT
31381 GTGGCTGCCG CCGCACCTCT AATGGTCGCG GGCAACACAC TCACCATGCA ATCACAGGCC
31441 CCGCTAACCG TGCACGACTC CAAACTTAGC ATTGCCACCC AAGGACCCCT CACAGTGTCA
31501 GAAGGAAAGC TAGCCCTGCA AACATCAGGC CCCCTCACCA CCACCGATAG CAGTACCCTT
31561 ACTATCACTG CCTCACCCCC TCTAACTACT GCCACTGGTA GCTTGGGCAT TGACTTGAAA
31621 GAGCCCATTT ATACACAAAA TGGAAAACTA GGACTAAAGT ACGGGGCTCC TTTGCATGTA
31681 ACAGACGACC TAAACACTTT GACCGTAGCA ACTGGTCCAG GTGTGACTAT TAATAATACT
31741 TCCTTGCAAA CTAAAGTTAC TGGAGCCTTG GGTTTTGATT CACAAGGCAA TATGCAACTT
31801 AATGTAGCAG GAGGACTAAG GATTGATTCT CAAAACAGAC GCCTTATACT TGATGTTAGT
31861 TATCCGTTTG ATGCTCAAAA CCAACTAAAT CTAAGACTAG GACAGGGCCC TCTTTTTATA
31921 AACTCAGCCC ACAACTTGGA TATTAACTAC AACAAAGGCC TTTACTTGTT TACAGCTTCA
31981 AACAATTCCA AAAAGCTTGA GGTTAACCTA AGCACTGCCA AGGGGTTGAT GTTTGACGCT
32041 ACAGCCATAG CCATTAATGC AGGAGATGGG CTTGAATTTG GTTCACCTAA TGCACCAAAC
32101 ACAAATCCCC TCAAAACAAA AATTGGCCAT GGCCTAGAAT TTGATTCAAA CAAGGCTATG
32161 GTTCCTAAAC TAGGAACTGG CCTTAGTTTT GACAGCACAG GTGCCATTAC AGTAGGAAAC
32221 AAAAATAATG ATAAGCTAAC TTTGTGGACC ACACCAGCTC CATCTCCTAA CTGTAGACTA
32281 AATGCAGAGA AAGATGCTAA ACTCACTTTG GTCTTAACAA AATGTGGCAG TCAAATACTT
32341 GCTACAGTTT CAGTTTTGGC TGTTAAAGGC AGTTTGGCTC CAATATCTGG AACAGTTCAA
32401 AGTGCTCATC TTATTATAAG ATTTGACGAA AATGGAGTGC TACTAAACAA TTCCTTCCTG
32461 GACCCAGAAT ATTGGAACTT TAGAAATGGA GATCTTACTG AAGGCACAGC CTATACAAAC
32521 GCTGTTGGAT TTATGCCTAA CCTATCAGCT TATCCAAAAT CTCACGGTAA AACTGCCAAA
32581 AGTAACATTG TCAGTCAAGT TTACTTAAAC GGAGACAAAA CTAAACCTGT AACACTAACC
32641 ATTACACTAA ACGGTACACA GGAAACAGGA GACACAACTC CAAGTGCATA CTCTATGTCA
32701 TTTTCATGGG ACTGGTCTGG CCACAACTAC ATTAATGAAA TATTTGCCAC ATCCTCTTAC
32761 ACTTTTTCAT ACATTGCCCA AGAATAAAGA ATCGTTTGTG TTATGTTTCA ACGTGTTTAT
32821 TTTTCAATTG CAGAAAATTT CAAGTCATTT TTCATTCAGT AGTATAGCCC CACCACCACA
32881 TAGCTTATAC AGATCACCGT ACCTTAATCA AACTCACAGA ACCCTAGTAT TCAACCTGCC
32941 ACCTCCCTCC CAACACACAG AGTACACAGT CCTTTCTCCC CGGCTGGCCT TAAAAAGCAT

FIG. 8J

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33001 CATATCATGG GTAACAGACA TATTCTTAGG TGTTATATTC CACACGGTTT CCTGTCGAGC
33061 CAAACGCTCA TCAGTGATAT TAATAAACTC CCCGGGCAGC TCACTTAAGT TCATGTCGCT
33121 GTCCAGCTGC TGAGCCACAG GCTGCTGTCC AACTTGCGGT TGCTTAACGG GCGGCGAAGG
33181 AGAAGTCCAC GCCTACATGG GGGTAGAGTC ATAATCGTGC ATCAGGATAG GGCGGTGGTG
33241 CTGCAGCAGC GCGCGAATAA ACTGCTGCCG CCGCCGCTCC GTCCTGCAGG AATACAACAT
33301 GGCAGTGGTC TCCTCAGCGA TGATTCGCAC CGCCCGCAGC ATAAGGCGCC TTGTCCTCCG
33361 GGCACAGCAG CGCACCCTGA TCTCACTTAA ATCAGCACAG TAACTGCAGC ACAGCACCAC
33421 AATATTGTTC AAAATCCCAC AGTGCAAGGC GCTGTATCCA AAGCTCATGG CGGGGACCAC
33481 AGAACCCACG TGGCCATCAT ACCACAAGCG CAGGTAGATT AAGTGGCGAC CCCTCATAAA
33541 CACGCTGGAC ATAAACATTA CCTCTTTTGG CATGTTGTAA TTCACCACCT CCCGGTACCA
33601 TATAAACCTC TGATTAAACA TGGCGCCATC CACCACCATC CTAAACCAGC TGGCCAAAAC
33661 CTGCCCGCCG GCTATACACT GCAGGGAACC GGGACTGGAA CAATGACAGT GGAGAGCCCA
33721 GGACTCGTAA CCATGGATCA TCATGCTCGT CATGATATCA ATGTTGGCAC AACACAGGCA
33781 CACGTGCATA CACTTCCTCA GGATTACAAG CTCCTCCCGC GTTAGAACCA TATCCCAGGG
33841 AACAACCCAT TCCTGAATCA GCGTAAATCC CACACTGCAG GGAAGACCTC GCACGTAACT
33901 CACGTTGTGC ATTGTCAAAG TGTTACATTC GGGCAGCAGC GGATGATCCT CCAGTATGGT
33961 AGCGCGGGTT TCTGTCTCAA AAGGAGGTAG ACGATCCCTA CTGTACGGAG TGCGCCGAGA
34021 CAACCGAGAT CGTGTTGGTC GTAGTGTCAT GCCAAATGGA ACGCCGGACG TAGTCATATT
34081 TCCTGAAGCA AAACCAGGTG CGGGCGTGAC AAACAGATCT GCGTCTCCGG TCTCGCCGCT
34141 TAGATCGCTC TGTGTAGTAG TTGTAGTATA TCCACTCTCT CAAAGCATCC AGGCGCCCCC
34201 TGGCTTCGGG TTCTATGTAA ACTCCTTCAT GCGCCGCTGC CCTGATAACA TCCACCACCG
34261 CAGAATAAGC CACACCCAGC CAACCTACAC ATTCGTTCTG CGAGTCACAC ACGGGAGGAG
34321 CGGGAAGAGC TGGAAGAACC ATGTTTTTTT TTTTATTCCA AAAGATTATC CAAAACCTCA
34381 AAATGAAGAT CTATTAAGTG AACGCGCTCC CCTCCGGTGG CGTGGTCAAA CTCTACAGCC
34441 AAAGAACAGA TAATGGCATT TGTAAGATGT TGCACAATGG CTTCCAAAAG GCAAACGGCC
34501 CTCACGTCCA AGTGGACGTA AAGGCTAAAC CCTTCAGGGT GAATCTCCTC TATAAACATT
34561 CCAGCACCTT CAACCATGCC CAAATAATTC TCATCTCGCC ACCTTCTCAA TATATCTCTA
34621 AGCAAATCCC GAATATTAAG TCCGGCCATT GTAAAAATCT GCTCCAGAGC GCCCTCCACC
34681 TTCAGCCTCA AGCAGCGAAT CATGATTGCA AAAATTCAGG TTCCTCACAG ACCTGTATAA
34741 GATTCAAAAG CGGAACATTA ACAAAAATAC CGCGATCCCG TAGGTCCCTT CGCAGGGCCA
34801 GCTGAACATA ATCGTGCAGG TCTGCACGGA CCAGCGCGGC CACTTCCCCG CCAGGAACCT
34861 TGACAAAAGA ACCCACACTG ATTATGACAC GCATACTCGG AGCTATGCTA ACCAGCGTAG
34921 CCCCGATGTA AGCTTTGTTG CATGGGCGGC GATATAAAAT GCAAGGTGCT GCTCAAAAAA
34981 TCAGGCAAAG CCTCGCGCAA AAAAGAAAGC ACATCGTAGT CATGCTCATG CAGATAAAGG
35041 CAGGTAAGCT CCGGAACCAC CACAGAAAAA GACACCATTT TTCTCTCAAA CATGTCTGCG
35101 GGTTTCTGCA TAAACACAAA ATAAAATAAC AAAAAAACAT TTAAACATTA GAAGCCTGTC
35161 TTACAACAGG AAAAACAACC CTTATAAGCA TAAGACGGAC TACGGCCATG CCGGCGTGAC
35221 CGTAAAAAAA CTGGTCACCG TGATTAAAAA GCACCACCGA CAGCTCCTCG GTCATGTCCG
35281 GAGTCATAAT GTAAGACTCG GTAAACACAT CAGGTTGATT CATCGGTCAG TGCTAAAAAG
35341 CGACCGAAAT AGCCCGGGGG AATACATACC CGCAGGCGTA GAGACAACAT TACAGCCCCC
35401 ATAGGAGGTA TAACAAAATT AATAGGAGAG AAAAACACAT AAACACCTGA AAAACCCTCC
35461 TGCCTAGGCA AAATAGCACC CTCCCGCTCC AGAACAACAT ACAGCGCTTC ACAGCGGCAG
35521 CCTAACAGTC AGCCTTACCA GTAAAAAAGA AAACCTATTA AAAAAACACC ACTCGACACG
35581 GCACCAGCTC AATCAGTCAC AGTGTAAAAA AGGGCCAAGT GCAGAGCGAG TATATATAGG
35641 ACTAAAAAAT GACGTAACGG TTAAAGTCCA CAAAAAACAC CCAGAAAACC GCACGCGAAC
35701 CTACGCCCAG AAACGAAAGC CAAAAAACCC ACAACTTCCT CAAATCGTCA CTTCCGTTTT
35761 CCCACGTTAC GTAACTTCCC ATTTTAAGAA AACTACAATT CCCAACACAT ACAAGTTACT
35821 CCGCCCTAAA ACCTACGTCA CCCGCCCCGT TCCCACGCCC CGCGCCACGT CACAAACTCC
35881 ACCCCCTCAT TATCATATTG GCTTCAATCC AAAATAAGGT ATATTATTGA TGATG
```

FIG. 8K

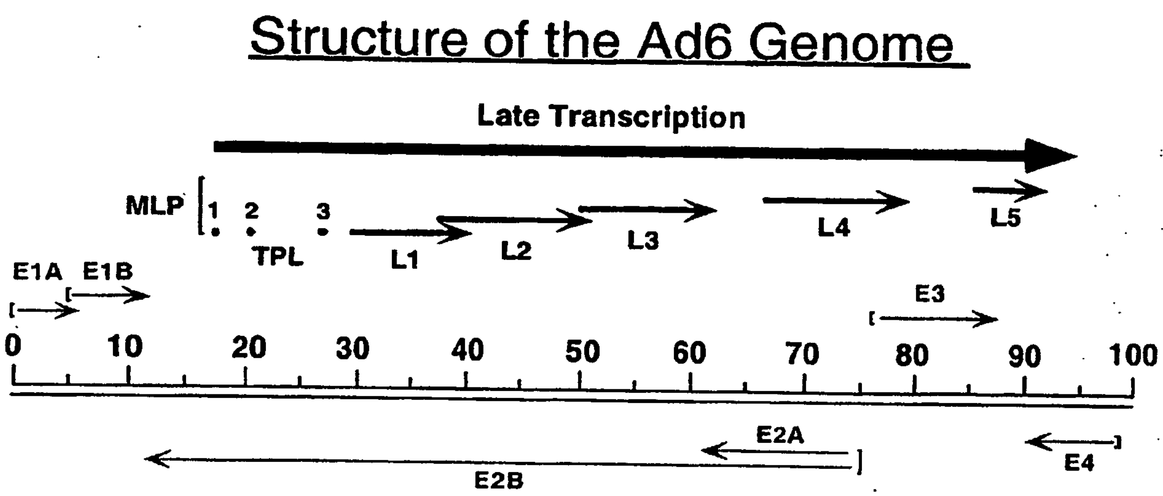

Structure of the Ad6 Genome
Late Transcription
MLP
1
2
3
TPL
L1
L2
L3
L4
L5
E1A
E1B
E3
0
10
20
30
40
50
60
70
80
90
100
E2A
E2B
E4

FIG. 9

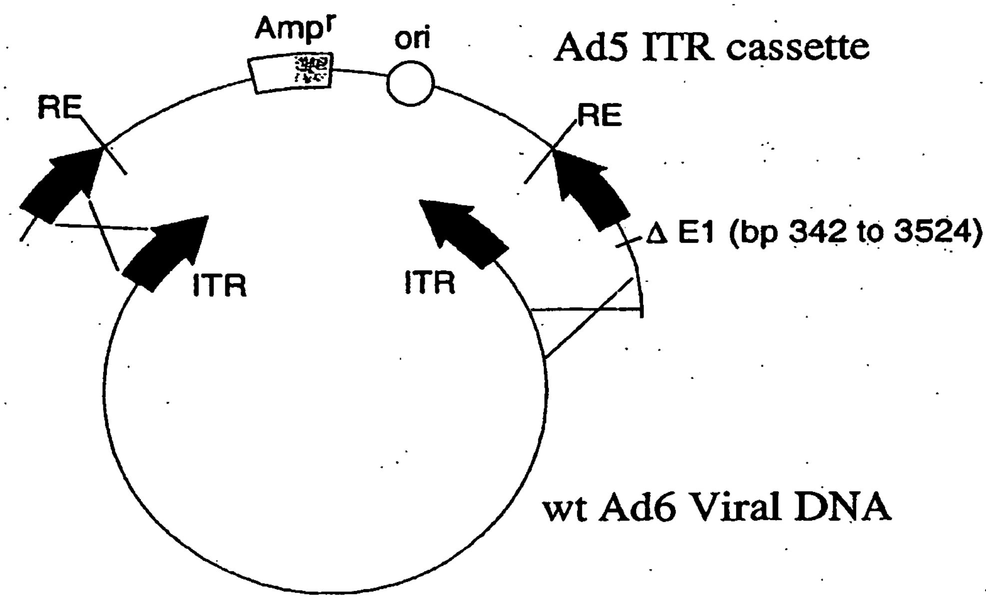

Amp^r
ori
Ad5 ITR cassette
RE
RE
Δ E1 (bp 342 to 3524)
ITR
ITR
wt Ad6 Viral DNA

FIG. 10

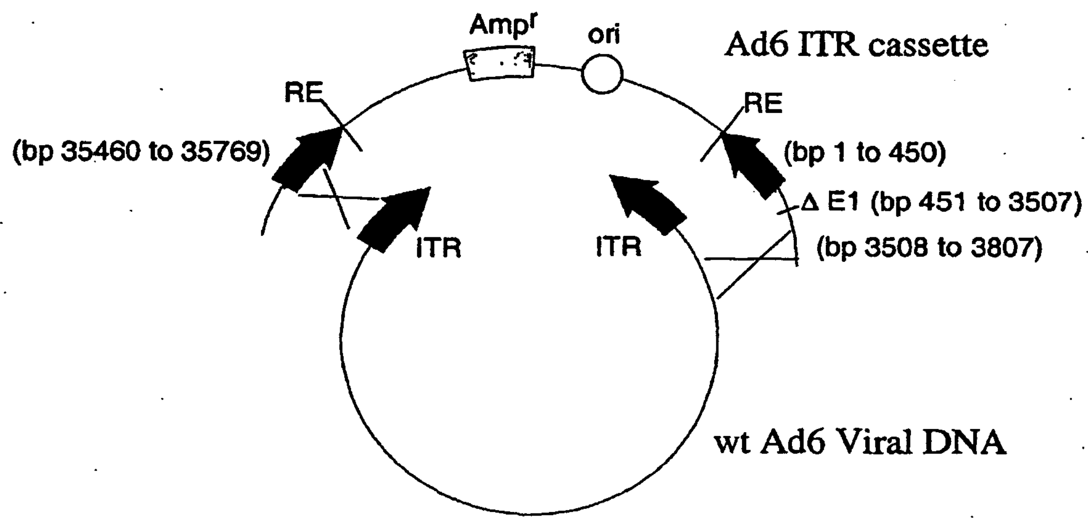
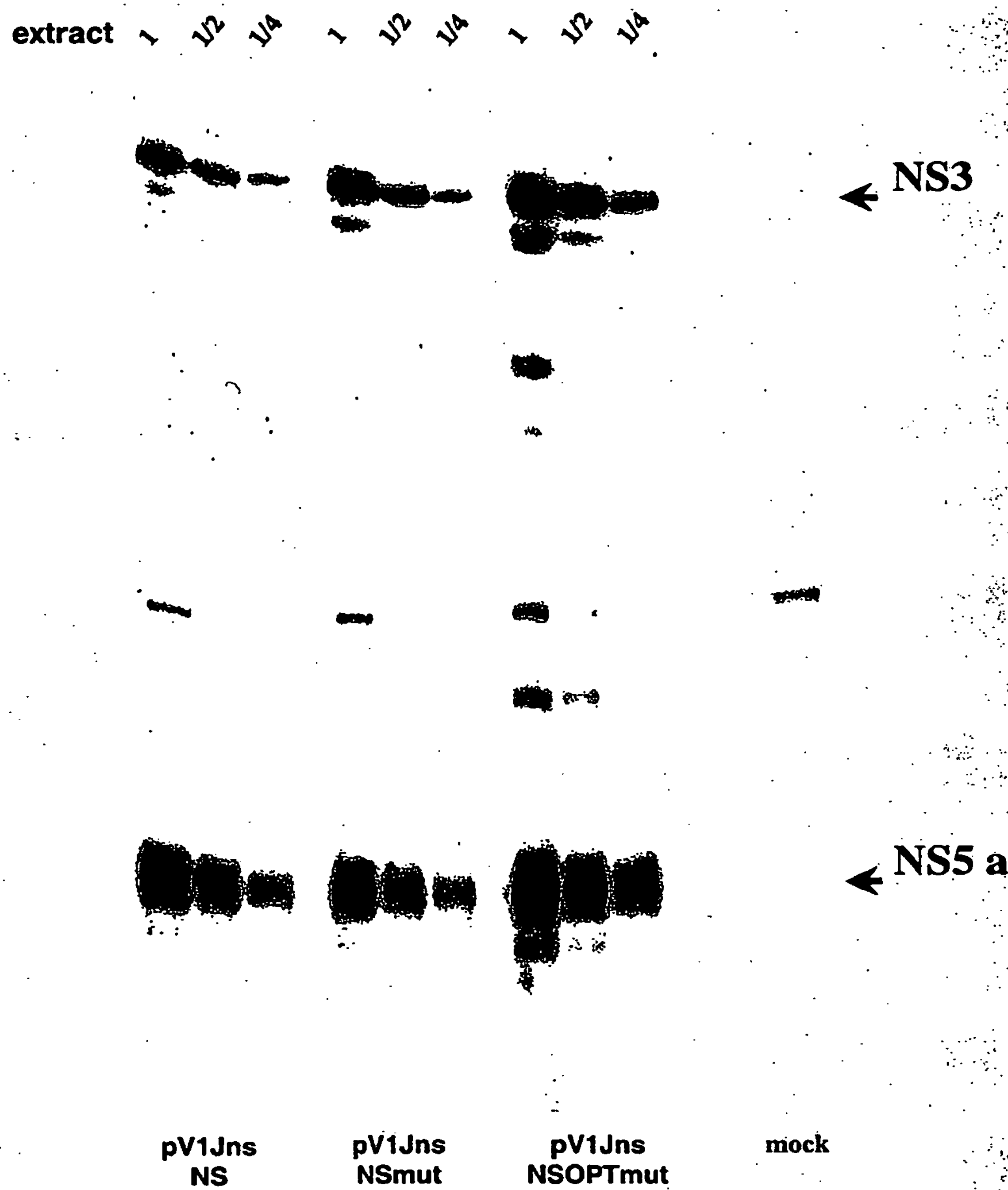

Ampr
ori
Ad6 ITR cassette
RE
RE
(bp 35460 to 35769)
(bp 1 to 450)
Δ E1 (bp 451 to 3507)
ITR
ITR
(bp 3508 to 3807)
wt Ad6 Viral DNA

FIG. 11



Western blot on whole-cell extracts from 293 cells transfected with plasmid DNA expressing the different HCV NS cassettes. Mature NS3 and NS5A products were detected with specific antibodies.

FIG. 12

pV1jns-NS

mouse	F(NS3p)	G(NS3h)	H(NS4)	I(NS5a)	L(NS35b)	M(NS5b)	1480(CD8 ep)	DMSO
	Pep pool							
#31	41	135	19	44	25	17	137	8
#32	121	783	77	144	13	22	604	4
#33	8	32	3	11	6	6	43	3
#34	16	139	13	47	31	25	151	2
#35	21	101	40	32	21	20	75	1
#36	18	26	24	25	5	7	29	6
#37	19	73	15	39	8	20	49	2
#38	133	575	74	345	75	63	515	5
#39	40	183	10	85	14	9	148	2
#40	66	465	29	111	15	16	189	0
Geomean	33	146	21	57	15	16	123	na

pV1jns-NSmut

mouse	F(NS3p)	G(NS3h)	H(NS4)	I(NS5a)	L(NS35b)	M(NS5b)	1480(CD8 ep)	DMSO
	Pep pool							
#41	39	293	58	187	5	4	248	1
#42	21	220	46	107	26	10	189	4
#43	76	134	12	78	8	6	144	2
#44	30	45	20	52	4	8	40	4
#45	36	100	17	56	4	6	116	3
#46	67	172	16	138	8	9	145	3
#47	34	131	28	38	9	5	118	1
#48	55	316	43	107	9	7	277	5
#49	6	131	5	25	4	1	91	0
#50	13	93	11	11	5	1	76	1
Geomean	30	142	20	61	7	5	126	na

V1jns-NSOPTmut

mouse	F(NS3p)	G(NS3h)	H(NS4)	I(NS5a)	L(NS35b)	M(NS5b)	1480(CD8 ep)	DMSO
	Pep pool							
#51	53	409	34	84	11	25	271	4
#52	140	660	65	276	23	36	377	2
#53	58	553	48	105	23	18	564	1
#54	50	105	35	134	10	16	80	2
#55	14	80	11	35	4	7	91	6
#56	14	342	30	101	23	14	207	1
#57	63	325	66	239	17	24	123	1
#58	75	542	66	168	127	93	191	0
#59	65	468	40	124	18	23	344	4
#60	27	142	48	16	7	8	77	0
Geomean	45	295	40	99	16	20	188	na

IFNγ ELIspot on splenocytes from C57black6 mice immunized with two injections of 25μg DNA/dose with GET of plasmid vectors expressing the different HCV NS cassettes. Data are expressed as SFC/10^6 PBMC.

FIG. 13A

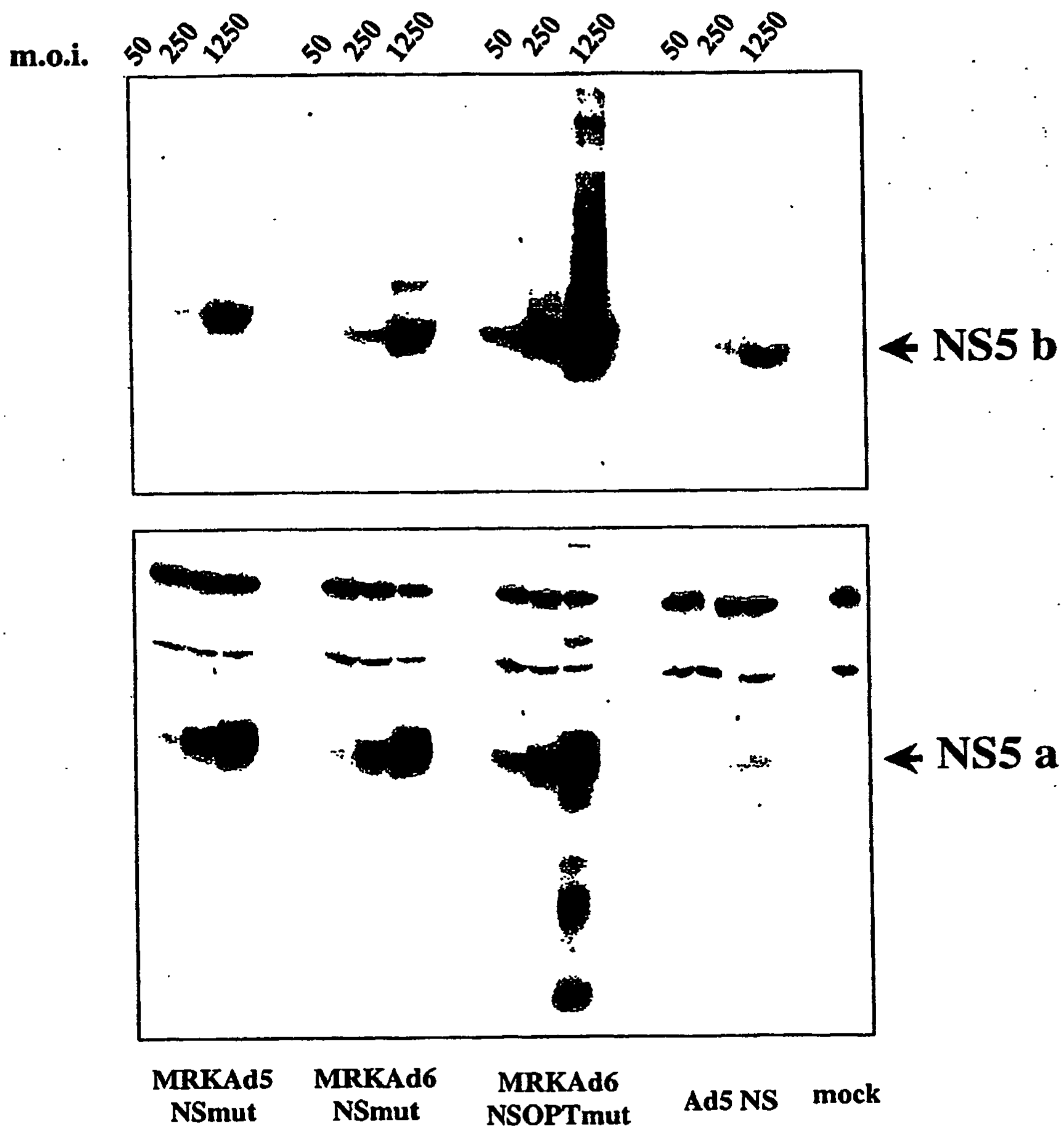
	mouse	F(NS3p)	G(NS3h)	H(NS4)	I(NS5a)	L(NS35b)	M(NS5b)	DMSO
		Pep pool						
pV1jns-NS	#51	219	699	634	486	487	264	34
	#52	67	302	347	167	111	87	9
	#53	59	460	400	246	244	136	26
	#54	139	817	685	236	547	223	24
	#55	96	904	542	277	256	337	17
	#56	225	603	686	156	350	240	56
	#57	44	288	211	148	100	141	4
	#58	37	262	221	53	58	62	3
	#59	131	975	928	159	305	284	14
	#60	93	475	464	77	206	113	12
	geo mean	111	579	512	201	266	189	20

	mouse	F(NS3p)	G(NS3h)	H(NS4)	I(NS5a)	L(NS35b)	M(NS5b)	DMSO
		Pep pool						
pV1jns-NSmut	#61	72	840	515	219	278	249	19
	#62	294	1881	1266	365	434	411	63
	#63	73	415	422	103	141	99	41
	#64	66	824	486	175	162	144	18
	#66	24	313	168	53	47	42	5
	#67	15	230	253	94	25	39	2
	#68	53	354	252	89	101	86	15
	#69	271	895	909	518	322	285	74
	#70	417	1303	1186	468	557	267	34
	geo mean	143	784	606	232	230	180	30

	mouse	F(NS3p)	G(NS3h)	H(NS4)	I(NS5a)	L(NS35b)	M(NS5b)	DMSO
		Pep pool						
V1jns-NSOPTmut	#71	206	944	890	342	207	397	47
	#72	393	1655	1151	575	626	401	72
	#73	123	522	515	319	223	198	21
	#74	500	1414	1419	878	1035	1122	137
	#75	286	812	873	382	543	267	31
	#76	224	1143	942	218	420	281	22
	#77	95	643	630	169	385	218	15
	#78	401	1302	1068	538	608	623	12
	#79	108	1190	914	199	265	215	4
	#80	122	511	546	189	286	190	13
	geo mean	209	941	854	331	406	329	24

IFNγ ELIspot on splenocytes from BalbC mice immunized with two injections of 50μg DNA/dose with GET of plasmid vectors expressing the different HCV NS cassettes. Data are expressed as SFC/10^6 PBMC.

FIG. 13B



Western blot on whole-cell extracts from HeLa cells infected at different multiplicity of infection (m.o.i.; indicated at the top) with Adenovectors expressing the different HCV NS cassettes. Mature NS5B and NS5A products were detected with specific antibodies.

FIG. 14

	mouse	F(NS3p)	G(NS3h)	H(NS4)	I(NS5a)	L+M(NS35b)	1480(CD8 ep)	DMSO
Ad5-NS	#1	14	492	9	27	10	554	7
	#2	8	440	2	26	5	438	0
	#3	12	92	5	12	7	73	4
	#4	16	388	6	40	6	228	2
	#6	8	210	4	31	3	238	3
	#7	7	133	13	16	0	128	9
	#8	11	342	25	55	22	267	12
	#9	5	345	0	45	5	285	3
	#10	22	888	3	65	25	799	1
	Geomean	10	305	na	31	na	269	na

Pep pool

	mouse	F(NS3p)	G(NS3h)	H(NS4)	I(NS5a)	L+M(NS35b)	1480(CD8 ep)	DMSO
MRKAd5-NSmut	#11	14	1009	13	75	7	751	6
	#12	15	695	3	39	9	552	1
	#13	12	389	4	20	7	352	3
	#14	7	459	6	50	1	274	1
	#15	5	549	3	22	6	485	0
	#16	10	631	1	6	4	600	3
	#17	5	257	3	9	1	245	3
	#18	13	659	6	43	7	555	1
	#19	12	758	1	37	5	669	0
	#20	22	1380	5	163	8	1003	4
	Geomean	10	615	3	31	4	504	na

Pep pool

	mouse	F(NS3p)	G(NS3h)	H(NS4)	I(NS5a)	L+M(NS35b)	1480(CD8 ep)	DMSO
MRKAd6-NSmut	#21	6	584	5	27	4	491	2
	#22	6	231	3	12	3	235	0
	#23	8	482	1	18	1	511	0
	#24	14	1120	6	38	10	1004	5
	#25	1	311	3	9	0	382	1
	#26	29	903	3	60	5	751	5
	#27	35	1573	4	40	4	1277	4
	#28	7	406	5	15	1	443	3
	#29	4	461	3	12	3	515	3
	Geomean	8	567	3	21	na	554	na

Pep pool

IFNγ ELISPOT on splenocytes from C57black6 mice immunized with two injections of 10^9 vp/dose of Adenovectors expressing the different HCV NS cassettes. Data are expressed as SFC/10^6 PBMC.

FIG. 15

Pep pools	Ad5-NS 10^{10} vp/dose		
	96074	*134T*	*063Q*
F (NS3p)	374	11	74
G (NS3h)	359	1070	1455
H (NS4)	376	30	64
I (NS5a)	240	40	63
L (NS5b)	226	29	121
M (NS5b)	511	23	35
DMSO	*128*	3	31

Pep pools	MRK Ad6-NSmut 10^{10} vp/dose		
	S207	*035Q*	*057Q*
F (NS3p)	363	382	150
G (NS3h)	180	316	119
H (NS4)	126	113	62
I (NS5a)	1780	688	114
L (NS5b)	447	111	81
M (NS5b)	153	38	16
DMSO	9	6	9

IFNγ ELISPOT on PBMC from Rhesus monkeys immunized with one injection of 10^{10} vp/dose of Adenovectors expressing the different HCV NS cassettes. Data are expressed as SFC/10^6 PBMC.

FIG. 16A

Pep pools	MRK Ad5-NSmut 10^{10} vp/dose		
	S201	*075Q*	*137Q*
F (NS3p)	928	69	254
G (NS3h)	317	436	98
H (NS4)	56	101	45
I (NS5a)	1530	1100	413
L (NS5b)	149	23	92
M (NS5b)	398	32	80
DMSO	29	6	29

Pep pools	MRK Ad6-NSOPTmut 10^{10} vp/dose		
	98D209	*106Q*	*113Q*
F (NS3p)	3110	263	404
G (NS3h)	2115	642	1008
H (NS4)	373	72	19
I (NS5a)	103	37	347
L (NS5b)	149	22	10
M (NS5b)	314	428	19
DMSO	0	1	3

IFNγ ELISPOT on PBMC from Rhesus monkeys immunized with one injection of 10^{10} vp/dose of Adenovectors expressing the different HCV NS cassettes. Data are expressed as SFC/10^6 PBMC.

FIG. 16B

Pep pools	Ad5-NS 10^{11} vp/dose			
	99C008	*97N104*	*97X008*	*99C026*
F (NS3p)	28	1026	579	889
G (NS3h)	1279	188	103	2453
H (NS4)	18	39	138	109
I (NS5a)	131	1068	172	141
L (NS5b)	78	144	103	32
M (NS5b)	24	68	47	84
DMSO	3	16	1	19

Pep pools	MRKAd6-NSmut 10^{11} vp/dose			
	98C047	*97C055*	*93G*	*97X014*
F (NS3p)	477	25	93	1022
G (NS3h)	959	398	81	1513
H (NS4)	36	14	99	53
I (NS5a)	171	45	1237	98
L (NS5b)	18	32	23	51
M (NS5b)	88	4	13	40
DMSO	8	3	1	5

IFNγ ELISPOT on PBMC from Rhesus monkeys immunized with two injections of 10^{11} vp/dose of Adenovectors expressing the different HCV NS cassettes. Data are expressed as SFC/10^6 PBMC.

FIG. 16C

	MRKAd5-NSmut 10^{11} vp/dose			
Pep pools	*99C059*	*99C060*	*97X009*	*96069*
F (NS3p)	28	81	1308	1618
G (NS3h)	2600	161	1008	123
H (NS4)	31	74	101	40
I (NS5a)	181	99	69	96
L (NS5b)	24	31	40	20
M (NS5b)	11	58	38	164
DMSO	6	15	1	16

IFNγ ELISPOT on PBMC from Rhesus monkeys immunized with two injections of 10^{11} vp/dose of Adenovectors expressing the different HCV NS cassettes. Data are expressed as SFC/10^6 PBMC.

FIG. 16D

Pep pools	MRK Ad5-NSmut 10^{10} vp/dose		
	S201	*075Q*	*137Q*
pool F (NS3p)	881	1755	73
pool G (NS3h)	573		
pool H (NS4)		3541	
pool I (NS5a)	2094		39
pool L (NS5b)			
pool M (NS5b)	756		
DMSO	*319*	*117*	*44*

Pep pools	MRK Ad6-NSOPTmut 10^{10} vp/dose		
	98D209	*106Q*	*113Q*
pool F (NS3p)	5073	84	952
pool G (NS3h)	2376	160	3325
pool H (NS4)	700		
pool I (NS5a)			1106
pool L (NS5b)			
pool M (NS5b)	530	706	
DMSO	43	47	28

Pep pools	MRK Ad6-NSmut 10^{10} vp/dose		
	S207	*035Q*	*057Q*
pool F (NS3p)	118	480	
pool G (NS3h)		196	
pool H (NS4)			
pool I (NS5a)	3340	933	
pool L (NS5b)	118		
pool M (NS5b)			
DMSO	145	34	

IFNγ ICS on PBMC from Rhesus monkeys immunized with two injections at four weeks interval with 10^{10} vp/dose of Adenovectors expressing the different HCV NS cassettes. Data are expressed as number of positive IFNγ/CD3/CD8 per 10^6 lymphocytes.

FIG. 17A

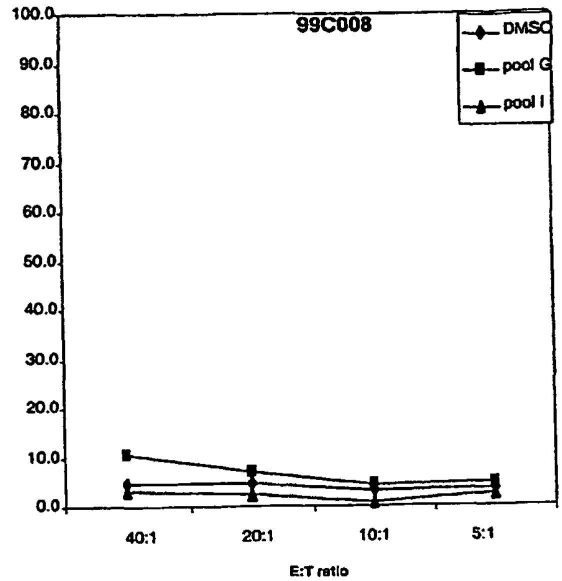
Pep pools	Ad5-NS 10^{11} vp/dose			
	99C008	97N104	97X008	99C026
F (NS3p)		1703	1136	615
G (NS3h)	3153			2787
H (NS4)				
I (NS5a)		2233		
L (NS5b)				
M (NS5b)				
DMSO	125	98	130	0

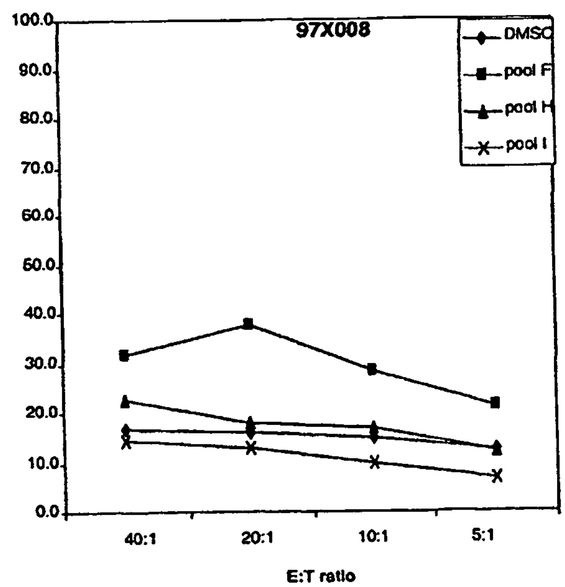
Pep pools	MRKAd6-NSmut 10^{11} vp/dose			
	98C047	97C055	93G	97X014
F (NS3p)	1024			948
G (NS3h)	3246	353		1074
H (NS4)			316	
I (NS5a)			6224	
L (NS5b)				
M (NS5b)				
DMSO	49	23	37	93

Pep pools	MRKAd5-NSmut 10^{11} vp/dose			
	99C059	99C060	97X009	96069
F (NS3p)			2266	5053
G (NS3h)	2434	316	1018	
H (NS4)				
I (NS5a)				
L (NS5b)				
M (NS5b)				205
DMSO	13	110	119	15

IFNγ ICS on PBMC from Rhesus monkeys immunized with two injections at four weeks interval with 10^{11} vp/dose of Adenovectors expressing the different HCV NS cassettes. Data are expressed as number of positive IFNγ/CD3/CD8 per 10^6 lymphocytes.

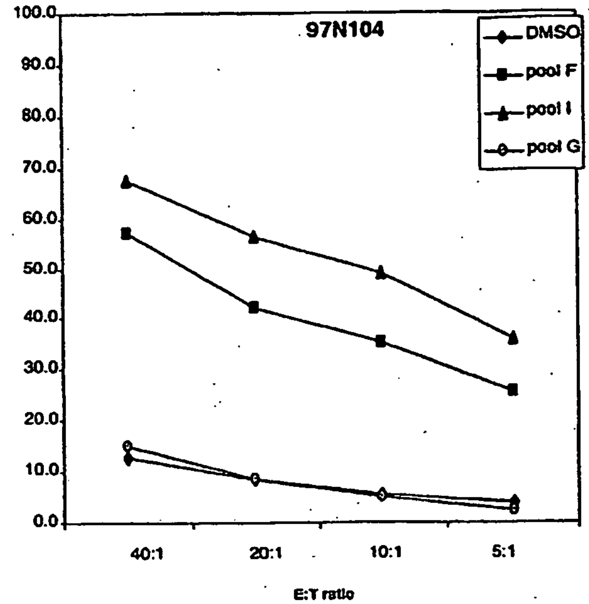
FIG. 17B

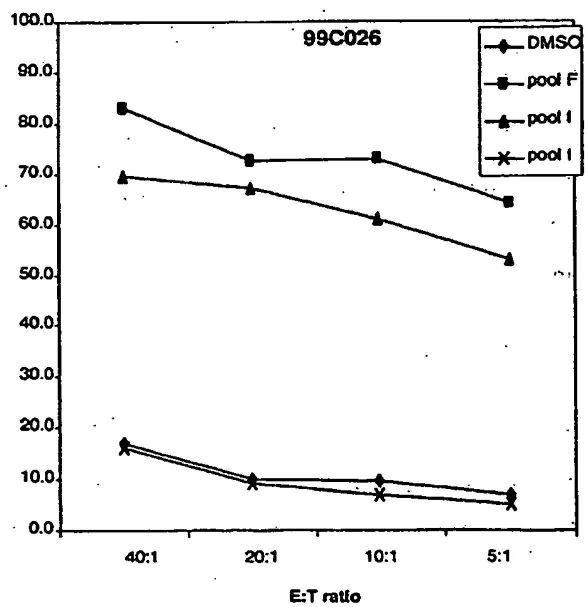




Bulk CTL assays on PBMC from Rhesus monkeys immunized with two injections of 10^{11}vp/dose of Ad5-NS.

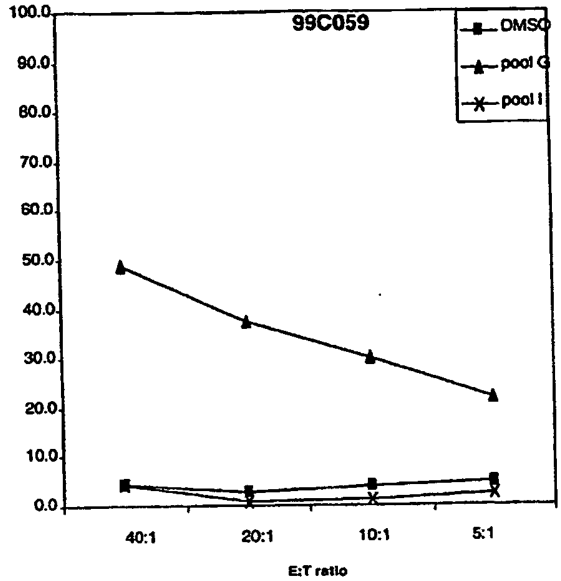
FIG. 18A

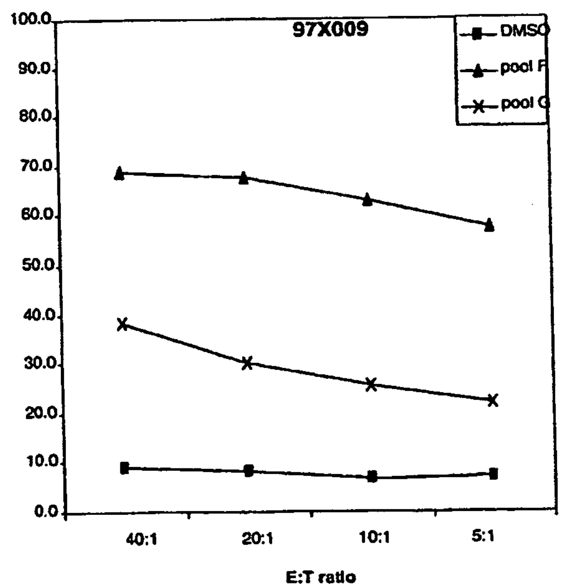




Bulk CTL assays on PBMC from Rhesus monkeys immunized with two injections of 10^{11}vp/dose of Ad5-NS.

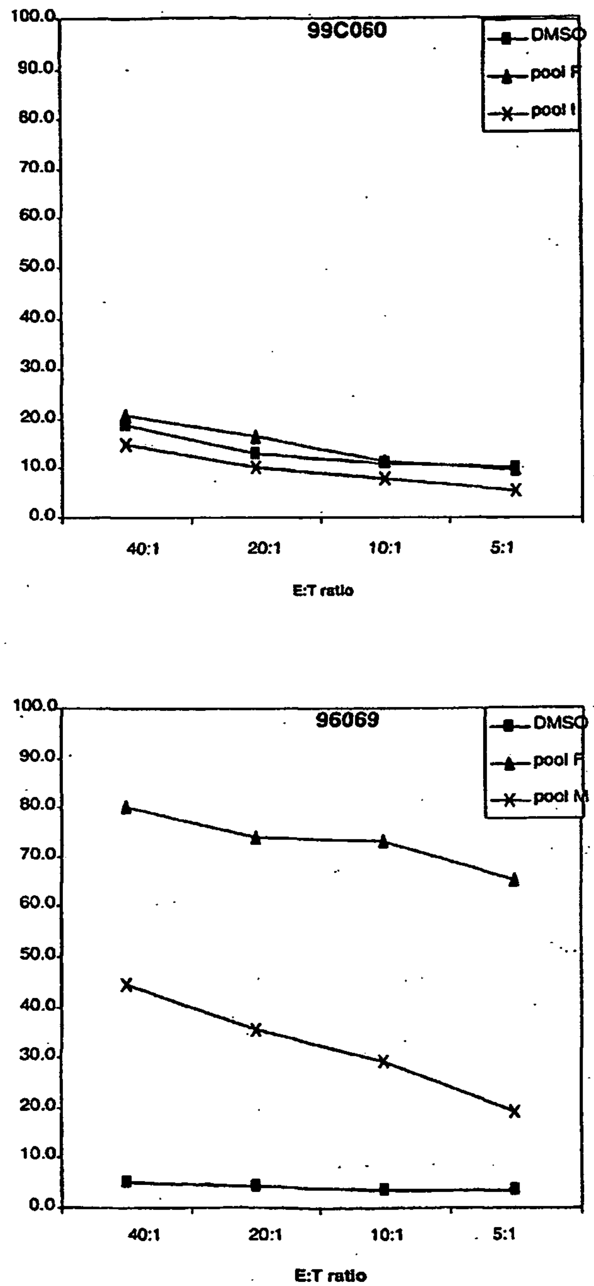
FIG. 18B





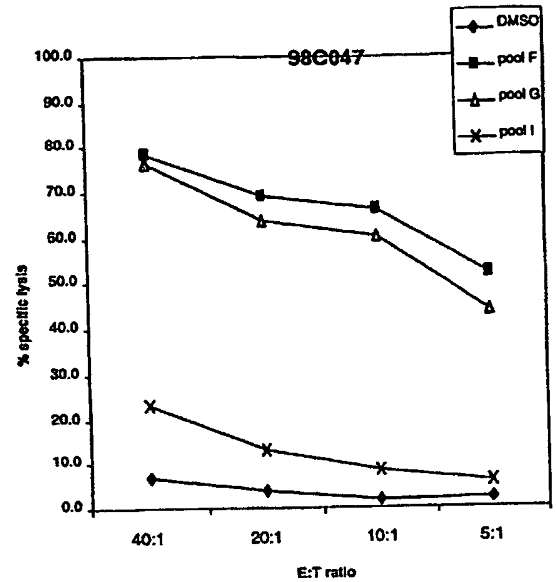
Bulk CTL assays on PBMC from Rhesus monkeys immunized with two injections of 10^{11}vp/dose of MRKAd5-NSmut.

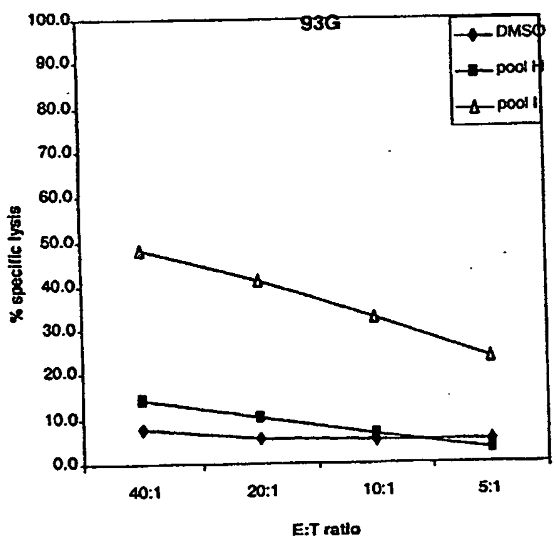
FIG. 18C



Bulk CTL assays on PBMC from Rhesus monkeys immunized with two injections of 10^{11}vp/dose of MRKAd5-NSmut

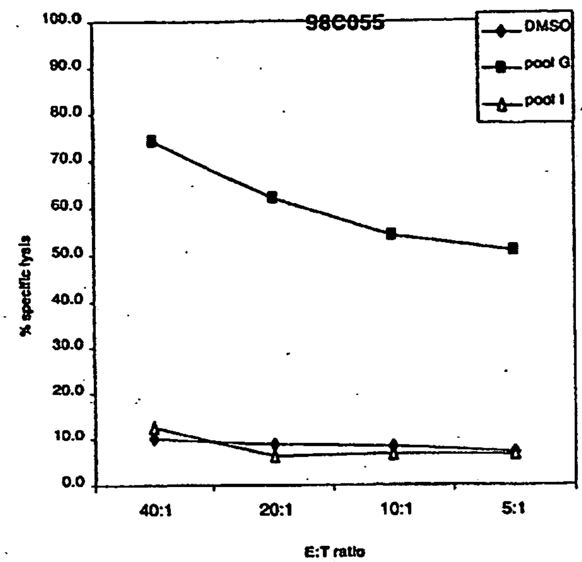
FIG. 18D

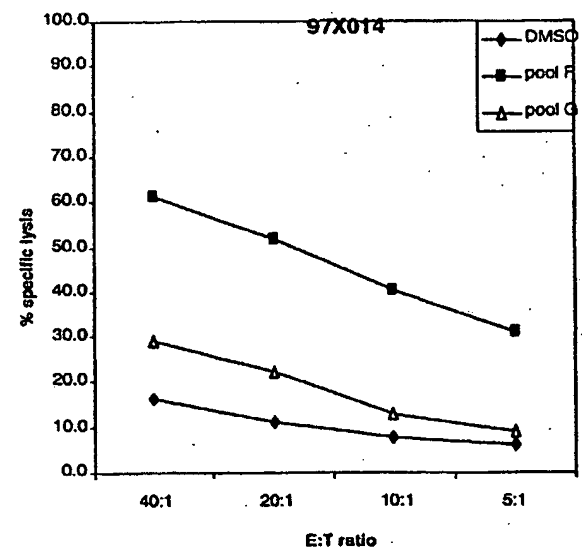




Bulk CTL assays on PBMC from Rhesus monkeys immunized with two injections of 10^{11}vp/dose of MRKAd6-NSmut.

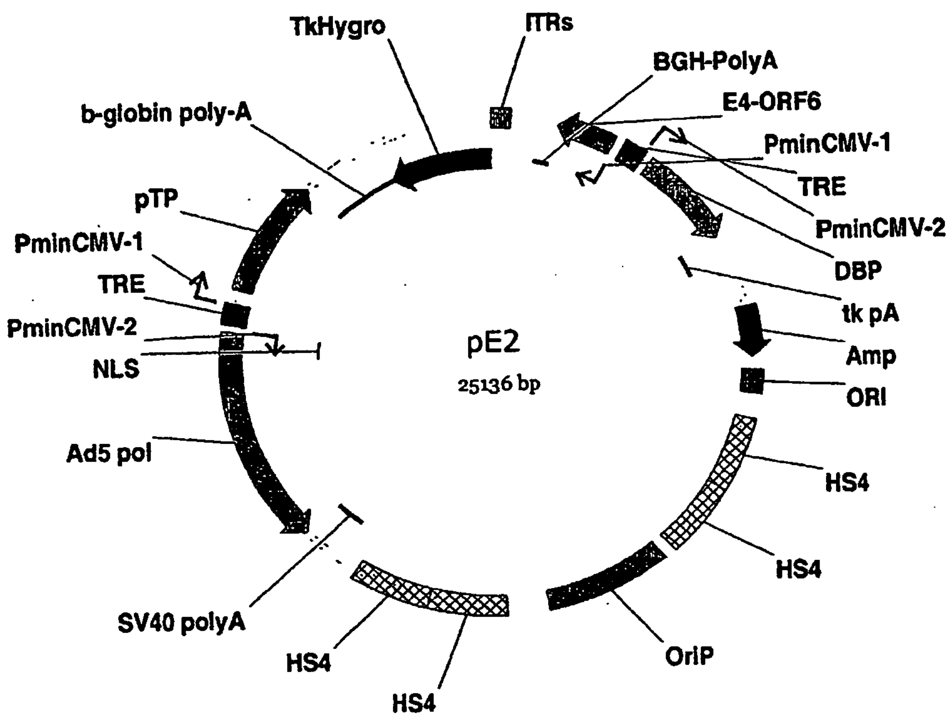
FIG. 18E





Bulk CTL assays on PBMC from Rhesus monkeys immunized with two injections of 10^{11}vp/dose of MRKAd6-NSmut.

FIG. 18F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E4-ORF6
PmInCMV-1
TRE
PmInCMV-2
DBP
tk pA
Amp
ORI
HS4
HS4
OriP
HS4
HS4
SV40 polyA
Ad5 pol
NLS
PminCMV-2
TRE
PminCMV-1
pTP
b-globin poly-A
pE2
25136 bp

FIG. 19

```
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  51 GGGCTGCATC ATCACCAGCC TGACCGGACG CGACAAGAAC CAGGTGGAGG
 101 GAGAGGTGCA GGTGGTGAGC ACCGCTACCC AGAGCTTCCT GGCCACCTGC
 151 GTGAACGGCG TGTGCTGGAC CGTGTACCAC GGAGCCGGAA GCAAGACCCT
 201 GGCCGGACCC AAGGGCCCTA TCACCCAGAT GTACACCAAT GTGGATCAGG
 251 ATCTGGTGGG CTGGCAGGCC CCTCCCGGAG CCAGGAGCCT GACACCCTGT
 301 ACCTGTGGAA GCAGCGACCT GTACCTGGTG ACACGCCACG CCGATGTGAT
 351 CCCCGTGAGG CGCAGGGGCG ATTCTCGCGG AAGCCTGCTG AGCCCTAGGC
 401 CCGTGAGCTA CCTGAAGGGC AGCAGCGGAG GACCCCTGCT GTGTCCTTCT
 451 GGCCATGCCG TGGGCATTTT TCGCGCTGCC GTGTGTACCA GGGGCGTGGC
 501 CAAAGCCGTG GATTTTGTGC CCGTGGAAAG CATGGAGACC ACCATGCGCA
 551 GCCCTGTGTT CACCGACAAC AGCTCTCCCC CTGCCGTGCC CCAATCATTC
 601 CAGGTGGCTC ACCTGCACGC CCCTACCGGA TCTGGCAAGA GCACCAAGGT
 651 GCCCGCTGCC TACGCCGCTC AGGGCTACAA GGTGCTGGTG CTGAACCCCA
 701 GCGTGGCCGC TACCCTGGGC TTCGGCGCTT ACATGAGCAA GGCCCATGGC
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 801 CGTGACCTAC AGCACCTACG GCAAGTTCCT GGCCGATGGA GGCTGCAGCG
 851 GAGGAGCCTA CGACATCATC ATCTGCGACG AGTGCCACAG CACCGACAGC
 901 ACCACCATCC TGGGCATTGG CACCGTGCTG GATCAGGCCG AAACAGCTGG
 951 AGCCAGGCTG GTGGTGCTGG CCACAGCTAC CCCTCCTGGC AGCGTGACCG
1001 TGCCCCATCC CAATATCGAG GAGGTGGCCC TGAGCAACAC AGGCGAGATC
1051 CCCTTCTACG GCAAGGCCAT CCCCATCGAG GCCATCCGCG GAGGCAGGCA
1101 CCTGATCTTC TGCCACAGCA AGAAGAAGTG CGACGAGCTG GCTGCCAAGC
1151 TGAGCGGACT GGGCATCAAC GCCGTGGCCT ACTACAGGGG CCTGGACGTG
1201 TCAGTGATCC CCACCATCGG CGATGTGGTG GTGGTGGCCA CCGACGCCCT
1251 GATGACAGGC TACACCGGAG ACTTCGACAG CGTGATCGAC TGCAACACCT
1301 GCGTGACCCA GACCGTGGAC TTCAGCCTGG ACCCCACCTT CACCATCGAA
1351 ACCACCACCG TGCCTCAGGA TGCTGTGAGC AGGAGCCAGA GGCGCGGACG
1401 CACCGGAAGG GGCAGGCGCG GAATTTATCG CTTTGTGACC CCTGGCGAAA
1451 GGCCCTCTGG CATGTTCGAC AGCAGCGTGC TGTGCGAGTG CTACGACGCT
1501 GGCTGCGCTT GGTACGAGCT GACACCCGCT GAAACCAGCG TGCGCCTGCG
1551 CGCTTATCTG AATACCCCTG GCCTGCCCGT GTGTCAGGAC CACCTGGAGT
```

FIG. 20A

1601 TCTGGGAGAG CGTGTTCACA GGACTGACCC ACATCGACGC CCATTTCCTG
1651 AGCCAGACCA AGCAGGCTGG CGACAACTTC CCCTATCTGG TGGCCTATCA
1701 GGCCACCGTG TGTGCTAGGG CCCAAGCTCC ACCTCCTTCA TGGGACCAGA
1751 TGTGGAAGTG CCTGATCCGC CTGAAGCCCA CCCTGCACGG CCCTACCCCT
1801 CTGCTGTACC GCCTGGGAGC CGTGCAGAAC GAGGTGACCC TGACCCACCC
1851 CATCACCAAG TACATCATGG CCTGCATGAG CGCTGATCTG GAAGTGGTGA
1901 CCAGCACCTG GGTGCTGGTG GGAGGCGTGC TGGCCGCTCT GGCTGCCTAC
1951 TGCCTGACCA CCGGAAGCGT GGTGATCGTG GGACGCATCA TCCTGAGCGG
2001 AAGGCCCGCT ATCGTGCCCG ATCGCGAGTT CCTGTACCAG GAGTTCGACG
2051 AGATGGAGGA GTGTGCCAGC CACCTGCCCT ACATCGAGCA GGGCATGCAG
2101 CTGGCCGAAC AGTTCAAGCA GAAGGCCCTG GGCCTGCTGC AGACAGCCAC
2151 CAAACAGGCC GAAGCTGCCG CTCCCGTGGT GGAAAGCAAG TGGAGGGCCC
2201 TGGAGACCTT CTGGGCTAAG CACATGTGGA ACTTCATCTC TGGCATCCAG
2251 TACCTGGCCG GACTGAGCAC CCTGCCTGGC AACCCCGCTA TCGCCAGCCT
2301 GATGGCCTTC ACCGCTAGCA TCACCTCTCC CCTGACCACC CAGAGCACCC
2351 TGCTGTTCAA CATTCTGGGC GGATGGGTGG CCGCTCAGCT GGCCCCTCCT
2401 TCAGCTGCTT CTGCCTTTGT GGGCGCTGGC ATTGCCGGAG CCGCTGTGGG
2451 CAGCATTGGC CTGGGCAAAG TGCTGGTGGA TATTCTGGCT GGCTATGGCG
2501 CTGGCGTGGC CGGAGCCCTG GTGGCCTTCA AGGTGATGAG CGGAGAGATG
2551 CCCAGCACCG AGGACCTGGT GAACCTGCTG CCTGCCATTC TGAGCCCTGG
2601 AGCCCTGGTG GTGGGCGTGG TGTGTGCTGC CATTCTGAGG CGCCATGTGG
2651 GACCCGGAGA GGGCGCTGTG CAGTGGATGA ACCGCCTGAT CGCCTTCGCC
2701 TCTCGCGGAA ACCACGTGAG CCCTACCCAC TACGTGCCTG AGAGCGACGC
2751 CGCTGCCAGG GTGACCCAGA TCCTGAGCAG CCTGACCATC ACCCAGCTGC
2801 TGAAGCGCCT GCACCAGTGG ATCAACGAGG ACTGCAGCAC ACCCTGCAGC
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2901 CTTCAAGACC TGGCTGCAGA GCAAGCTGCT GCCCCAACTG CCTGGCGTGC
2951 CCTTCTTCTC ATGCCAGCGC GGATACAAGG GCGTGTGGAG GGGCGATGGC
3001 ATCATGCAGA CCACCTGTCC CTGCGGAGCC CAGATCACAG GCCACGTGAA
3051 GAACGGCAGC ATGCGCATCG TGGGCCCTAA GACCTGCAGC AACACCTGGC
3101 ACGGCACCTT CCCCATCAAC GCCTACACCA CCGGACCCTG CACACCCAGC
3151 CCTGCTCCCA ACTACAGCAG GGCCCTGTGG AGGGTGGCTG CCGAGGAGTA

FIG. 20B

3201 CGTGGAGGTG ACCAGGGTGG GAGACTTCCA CTACGTGACC GGAATGACCA
3251 CCGACAACGT GAAGTGTCCC TGTCAGGTGC CCGCTCCCGA ATTTTTTACC
3301 GAAGTGGATG GCGTGCGCCT GCATCGCTAT GCCCCTGCCT GTAGGCCCCT
3351 GCTGCGCGAA GAAGTGACCT TCCAGGTGGG CCTGAACCAG TACCTGGTGG
3401 GCAGCCAGCT GCCCTGCGAG CCTGAGCCCG ATGTGGCCGT GCTGACCAGC
3451 ATGCTGACCG ACCCCAGCCA CATCACAGCC GAAACCGCTA AAAGGCGCCT
3501 GGCCAGGGGC TCTCCTCCAA GCCTGGCCTC AAGCAGCGCT AGCCAGCTGT
3551 CTGCTCCCAG CCTGAAGGCC ACCTGCACCA CCCACCACGT GAGCCCCGAC
3601 GCCGACCTGA TCGAGGCCAA CCTGCTGTGG CGCCAGGAGA TGGGCGGCAA
3651 CATCACCCGC GTGGAGAGCG AGAACAAGGT GGTGGTGCTG GACAGCTTCG
3701 ACCCCCTGCG CGCCGAGGAG GACGAGCGCG AGGTGAGCGT GCCCGCCGAG
3751 ATCCTGCGCA AGAGCAAGAA GTTCCCCGCT GCCATGCCCA TCTGGGCTAG
3801 ACCTGATTAC AACCCTCCCC TGCTGGAGAG CTGGAAGGAC CCTGATTACG
3851 TGCCTCCAGT GGTGCATGGC TGTCCTCTGC CTCCCATTAA AGCCCCTCCT
3901 ATTCCACCTC CTAGGCGCAA AAGGACCGTG GTGCTGACAG AAAGCAGCGT
3951 GAGCTCTGCT CTGGCCGAAC TGGCCACCAA GACCTTTGGC AGCAGCGAGA
4001 GCTCTGCCGT GGACAGCGGA ACAGCCACCG CTCTGCCTGA CCAGGCCAGC
4051 GACGACGGCG ATAAGGGCAG CGATGTGGAG AGCTATAGCA GCATGCCTCC
4101 CCTGGAAGGC GAACCTGGCG ATCCCGATCT GAGCGATGGC AGCTGGAGCA
4151 CCGTGAGCGA AGAGGCCAGC GAGGACGTGG TGTGTTGCAG CATGAGCTAC
4201 ACCTGGACAG GCGCTCTGAT CACACCCTGC GCTGCCGAGG AGAGCAAGCT
4251 GCCCATCAAC GCCCTGAGCA ACAGCCTGCT GAGGCACCAC AACATGGTGT
4301 ACGCCACCAC CAGCAGGTCT GCCGGACTGA GGCAGAAGAA GGTGACCTTC
4351 GACCGCCTGC AGGTGCTGGA CGACCACTAC CGCGATGTGC TGAAGGAGAT
4401 GAAGGCCAAG GCCAGCACCG TGAAGGCCAA GCTGCTGAGC GTGGAGGAGG
4451 CCTGCAAGCT GACCCCCCCC CACAGCGCCA AGAGCAAGTT CGGCTACGGC
4501 GCCAAGGACG TGCGCAACCT GAGCAGCAAG GCCGTGAACC ACATCCACAG
4551 CGTGTGGAAG GACCTGCTGG AGGACACCGT GACCCCCATC GACACCACCA
4601 TCATGGCCAA GAACGAGGTG TTCTGCGTGC AGCCCGAGAA GGGCGGCCGC
4651 AAGCCCGCTC GCCTGATCGT GTTCCCCGAT CTGGGCGTGC GCGTGTGCGA
4701 GAAGATGGCC CTGTACGACG TGGTGAGCAC CCTGCCTCAG GTGGTGATGG
4751 GCTCAAGCTA CGGCTTCCAG TACAGCCCTG GCCAGCGCGT GGAGTTCCTG

FIG. 20C

4801 GTGAACACCT GGAAGAGCAA GAAGAACCCC ATGGGCTTCA GCTACGACAC
4851 ACGCTGCTTC GACAGCACCG TGACCGAGAA CGACATCCGC GTGGAGGAGA
4901 GCATCTACCA GTGCTGCGAC CTGGCCCCTG AGGCCAGGCA GGCCATCAAG
4951 AGCCTGACCG AGCGCCTGTA CATCGGAGGC CCTCTGACCA ACAGCAAGGG
5001 ACAGAACTGC GGATACAGGC GCTGTAGGGC CTCTGGCGTG CTGACCACCA
5051 GCTGTGGCAA CACCCTGACC TGCTACCTGA AGGCCAGCGC TGCCTGTCGC
5101 GCTGCCAAGC TGCAGGACTG CACCATGCTG GTGAACGCCG CTGGCCTGGT
5151 GGTGATTTGT GAAAGCGCTG GCACCCAGGA AGATGCTGCC AGCCTGCGCG
5201 TGTTCACCGA GGCCATGACC AGGTACTCTG CCCCTCCCGG AGACCCCCCT
5251 CAGCCCGAAT ACGACCTGGA GCTGATCACC AGCTGCTCAA GCAACGTGAG
5301 CGTGGCTCAC GACGCCAGCG GAAAGCGCGT GTACTACCTG ACACGCGATC
5351 CCACCACCCC TCTGGCTCGC GCTGCCTGGG AAACCGCTCG CCATACACCC
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5551 GAGCCCCTGG ACCTGCCCCA AATCATCGAG CGCCTGCACG GCCTGTCTGC
5601 CTTCAGCCTG CACAGCTACA GCCCTGGCGA AATTAATCGC GTGGCCAGCT
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5701 AGGAGCGTGA GGGCTAGGCT GCTGAGCCAG GGAGGCAGGG CCGCTACCTG
5751 TGGAAAGTAC CTGTTCAACT GGGCCGTGAA GACCAAGCTG AAGCTGACCC
5801 CTATCCCTGC CGCTAGCCAG CTGGACCTGA GCGGATGGTT CGTGGCTGGC
5851 TACAGCGGAG GCGACATCTA CCACAGCCTG TCTCGCGCTC GCCCTCGCTG
5901 GTTCATGCTG TGCCTGCTGC TGCTGAGCGT GGGCGTGGGC ATCTACCTGC
5951 TGCCCAACCG CTAAA

FIG. 20D

IN THE PCT RECEIVING OFFICE
OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Merck & Co., Inc		
PCT Serial No.:	To Be Assigned	Case No.: PCT ITR0015Y	US/RO
Filing date:	On Even Date Herewith		Authorized Officer:
For:	HEPATITIS C VIRUS VACCINE		To Be Assigned

Assistant Commissioner of Patents
BOX PCT
Washington, D.C. 20231

NUCLEOTIDE AND/OR AMINO ACID
SEQUENCE DISCLOSURE, PCT RULE 5.2

Sir:

As required under PCT Rule 5.2, Applicant respectfully encloses a paper (64 pages) and a computer readable form of the Sequence Listing for the above-identified PCT International Application, filed on even date herewith.

I hereby state that the content of the paper and computer readable forms of the Sequence Listing, submitted in accordance with WIPO and Standard ST.23 and under PCT Rule 13ter.1, respectively, are the same.

Respectfully submitted,

By [signature]

Sheldon O. Heber
Reg. No. 38,179
Attorney for Applicants

Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0907
(732) 594-1958

SEQUENCE LISTING

<110> Merck & Co. Inc., and Istituto Di Ricerche Di Biologia Molecolare P. Angeletti S.P.A.

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Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr Cys
        35                  40                  45
Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys Thr
    50                  55                  60
Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val Asp
65                  70                  75                  80
Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu Thr
                85                  90                  95
Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala
            100                 105                 110
Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu
        115                 120                 125
Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro Leu
    130                 135                 140
Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys
145                 150                 155                 160
Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met
                165                 170                 175
Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro Pro
            180                 185                 190
Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr Gly
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Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly
245 250 255
Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr Tyr Gly
260 265 270
Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile
275 280 285
Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu Gly Ile
290 295 300
Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val
305 310 315 320
Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn
325 330 335
Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe Tyr Gly
340 345 350
Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu Ile Phe
355 360 365
Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Ser Gly
370 375 380
Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val
385 390 395 400
Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met
405 410 415
Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys
420 425 430
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435 440 445
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485 490 495
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500 505 510
Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys Gln Asp
515 520 525
His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His Ile Asp
530 535 540
Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe Pro Tyr
545 550 555 560
Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro
565 570 575
Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr
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595 600 605
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Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu Gly
            20                  25                  30

gag gtt cag gtg gtt tcc acc gca aca caa tcc ttc ctg gcg acc tgc     144
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Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr Cys
35 40 45

gtc aac ggc gtg tgt tgg acc gtt tac cat ggt gct ggc tca aag acc 192
Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys Thr
50 55 60

tta gcc ggc cca aag ggg cca atc acc cag atg tac act aat gtg gac 240
Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val Asp
65 70 75 80

cag gac ctc gtc ggc tgg cag gcg ccc ccc ggg gcg cgt tcc ttg aca 288
Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu Thr
85 90 95

cca tgc acc tgt ggc agc tca gac ctt tac ttg gtc acg aga cat gct 336
Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala
100 105 110

gac gtc att ccg gtg cgc cgg cgg ggc gac agt agg ggg agc ctg ctc 384
Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu
115 120 125

tcc ccc agg cct gtc tcc tac ttg aag ggc tct tcg ggt ggt cca ctg 432
Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro Leu
130 135 140

ctc tgc cct tcg ggg cac gct gtg ggc atc ttc cgg gct gcc gta tgc 480
Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys
145 150 155 160

acc cgg ggg gtt gcg aag gcg gtg gac ttt gtg ccc gta gag tcc atg 528
Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met
165 170 175

gaa act act atg cgg tct ccg gtc ttc acg gac aac tca tcc ccc ccg 576
Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro Pro
180 185 190

gcc gta ccg cag tca ttt caa gtg gcc cac cta cac gct ccc act ggc 624
Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr Gly
195 200 205

agc ggc aag agt act aaa gtg ccg gct gca tat gca gcc caa ggg tac 672
Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln Gly Tyr
210 215 220

aag gtg ctc gtc ctc aat ccg tcc gtt gcc gct acc tta ggg ttt ggg 720
Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly
225 230 235 240

gcg tat atg tct aag gca cac ggt att gac ccc aac atc aga act ggg 768
Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly
245 250 255

gta agg acc att acc aca ggc gcc ccc gtc aca tac tct acc tat ggc 816
Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr Tyr Gly
260 265 270

aag ttt ctt gcc gat ggt ggt tgc tct ggg ggc gct tat gac atc ata 864
Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile
275 280 285

ata tgt gat gag tgc cat tca act gac tcg act aca atc ttg ggc atc 912
Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu Gly Ile
290 295 300

ggc aca gtc ctg gac caa gcg gag acg gct gga gcg cgg ctt gtc gtg 960
Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val
305 310 315 320

ctc gcc acc gct acg cct ccg gga tcg gtc acc gtg cca cac cca aac 1008
Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn
325 330 335

atc gag gag gtg gcc ctg tct aat act gga gag atc ccc ttc tat ggc 1056
Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe Tyr Gly
340 345 350

aaa gcc atc ccc att gaa gcc atc agg ggg gga agg cat ctc att ttc 1104
Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu Ile Phe
355 360 365

tgt cat tcc aag aag aag tgc gac gag ctc gcc gca aag ctg tca ggc 1152
Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Ser Gly
370 375 380

ctc gga atc aac gct gtg gcg tat tac cgg ggg ctc gat gtg tcc gtc 1200
Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val
385 390 395 400

ata cca act atc gga gac gtc gtt gtc gtg gca aca gac gct ctg atg 1248
Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met
405 410 415

acg ggc tat acg ggc gac ttt gac tca gtg atc gac tgt aac aca tgt 1296
Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys
420 425 430

gtc acc cag aca gtc gac ttc agc ttg gat ccc acc ttc acc att gag 1344
Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu
435 440 445

acg acg acc gtg cct caa gac gca gtg tcg cgc tcg cag cgg cgg ggt 1392
Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg Arg Gly
450 455 460

agg act ggc agg ggt agg aga ggc atc tac agg ttt gtg act ccg gga 1440
Arg Thr Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr Pro Gly
465 470 475 480

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gaa cgg ccc tcg ggc atg ttc gat tcc tcg gtc ctg tgt gag tgc tat      1488
Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr
                485                 490                 495

gac gcg ggc tgt gct tgg tac gag ctc acc ccc gcc gag acc tcg gtt      1536
Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Ser Val
            500                 505                 510

agg ttg cgg gcc tac ctg aac aca cca ggg ttg ccc gtt tgc cag gac      1584
Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys Gln Asp
        515                 520                 525

cac ctg gag ttc tgg gag agt gtc ttc aca ggc ctc acc cac ata gat      1632
His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His Ile Asp
    530                 535                 540

gca cac ttc ttg tcc cag acc aag cag gca gga gac aac ttc ccc tac      1680
Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe Pro Tyr
545                 550                 555                 560

ctg gta gca tac caa gcc acg gtg tgc gcc agg gct cag gcc cca cct      1728
Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro
                565                 570                 575

cca tca tgg gat caa atg tgg aag tgt ctc ata cgg ctg aaa cct acg      1776
Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr
            580                 585                 590

ctg cac ggg cca aca ccc ttg ctg tac agg ctg gga gcc gtc caa aat      1824
Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn
        595                 600                 605

gag gtc acc ctc acc cac ccc ata acc aaa tac atc atg gca tgc atg      1872
Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala Cys Met
    610                 615                 620

tcg gct gac ctg gag gtc gtc act agc acc tgg gtg ctg gtg ggc gga      1920
Ser Ala Asp Leu Glu Val Val Thr Ser Thr Trp Val Leu Val Gly Gly
625                 630                 635                 640

gtc ctt gca gct ctg gcc gcg tat tgc ctg aca aca ggc agt gtg gtc      1968
Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Thr Thr Gly Ser Val Val
                645                 650                 655

att gtg ggt agg att atc ttg tcc ggg agg ccg gct att gtt ccc gac      2016
Ile Val Gly Arg Ile Ile Leu Ser Gly Arg Pro Ala Ile Val Pro Asp
            660                 665                 670

agg gag ttt ctc tac cag gag ttc gat gaa atg gaa gag tgc gcc tcg      2064
Arg Glu Phe Leu Tyr Gln Glu Phe Asp Glu Met Glu Glu Cys Ala Ser
        675                 680                 685

cac ctc cct tac atc gag cag gga atg cag ctc gcc gag caa ttc aag      2112
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His Leu Pro Tyr Ile Glu Gln Gly Met Gln Leu Ala Glu Gln Phe Lys
690 695 700

cag aaa gcg ctc ggg tta ctg caa aca gcc acc aaa caa gcg gag gct 2160
Gln Lys Ala Leu Gly Leu Leu Gln Thr Ala Thr Lys Gln Ala Glu Ala
705 710 715 720

gct gct ccc gtg gtg gag tcc aag tgg cga gcc ctt gag aca ttc tgg 2208
Ala Ala Pro Val Val Glu Ser Lys Trp Arg Ala Leu Glu Thr Phe Trp
725 730 735

gcg aag cac atg tgg aat ttc atc agc ggg ata cag tac tta gca ggc 2256
Ala Lys His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala Gly
740 745 750

tta tcc act ctg cct ggg aac ccc gca ata gca tca ttg atg gca ttc 2304
Leu Ser Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu Met Ala Phe
755 760 765

aca gcc tct atc acc agc ccg ctc acc acc caa agt acc ctc ctg ttt 2352
Thr Ala Ser Ile Thr Ser Pro Leu Thr Thr Gln Ser Thr Leu Leu Phe
770 775 780

aac atc ttg ggg ggg tgg gtg gct gcc caa ctc gcc ccc ccc agc gcc 2400
Asn Ile Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Pro Pro Ser Ala
785 790 795 800

gct tcg gct ttc gtg ggc gcc ggc atc gcc ggt gcg gct gtt ggc agc 2448
Ala Ser Ala Phe Val Gly Ala Gly Ile Ala Gly Ala Ala Val Gly Ser
805 810 815

ata ggc ctt ggg aag gtg ctt gtg gac att ctg gcg ggt tat gga gca 2496
Ile Gly Leu Gly Lys Val Leu Val Asp Ile Leu Ala Gly Tyr Gly Ala
820 825 830

gga gtg gcc ggc gcg ctc gtg gcc ttc aag gtc atg agc ggc gag atg 2544
Gly Val Ala Gly Ala Leu Val Ala Phe Lys Val Met Ser Gly Glu Met
835 840 845

ccc tcc acc gag gac ctg gtc aat cta ctt cct gcc atc ctc tct cct 2592
Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro
850 855 860

ggc gcc ctg gtc gtc ggg gtc gtg tgt gca gca ata ctg cgt cga cac 2640
Gly Ala Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg His
865 870 875 880

gtg ggt ccg gga gag ggg gct gtg cag tgg atg aac cgg ctg ata gcg 2688
Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala
885 890 895

ttc gcc tcg cgg ggt aat cat gtt tcc ccc acg cac tat gtg cct gag 2736
Phe Ala Ser Arg Gly Asn His Val Ser Pro Thr His Tyr Val Pro Glu
900 905 910

agc gac gcc gca gcg cgt gtt act cag atc ctc tcc agc ctt acc atc 2784
Ser Asp Ala Ala Ala Arg Val Thr Gln Ile Leu Ser Ser Leu Thr Ile
915 920 925

act cag ctg ctg aaa agg ctc cac cag tgg att aat gaa gac tgc tcc 2832
Thr Gln Leu Leu Lys Arg Leu His Gln Trp Ile Asn Glu Asp Cys Ser
930 935 940

aca ccg tgt tcc ggc tcg tgg cta agg gat gtt tgg gac tgg ata tgc 2880
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945 950 955 960

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Thr Val Leu Thr Asp Phe Lys Thr Trp Leu Gln Ser Lys Leu Leu Pro
965 970 975

cag cta ccg gga gtc cct ttt ttc tcg tgc caa cgc ggg tac aag gga 2976
Gln Leu Pro Gly Val Pro Phe Phe Ser Cys Gln Arg Gly Tyr Lys Gly
980 985 990

gtc tgg cgg gga gac ggc atc atg caa acc acc tgc cca tgt gga gca 3024
Val Trp Arg Gly Asp Gly Ile Met Gln Thr Thr Cys Pro Cys Gly Ala
995 1000 1005

cag atc acc gga cat gtc aaa aac ggt tcc atg agg atc gtc ggg cct 3072
Gln Ile Thr Gly His Val Lys Asn Gly Ser Met Arg Ile Val Gly Pro
1010 1015 1020

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Lys Thr Cys Ser Asn Thr Trp His Gly Thr Phe Pro Ile Asn Ala Tyr
1025 1030 1035 1040

acc acg ggc ccc tgc aca ccc tct cca gcg cca aac tat tct agg gcg 3168
Thr Thr Gly Pro Cys Thr Pro Ser Pro Ala Pro Asn Tyr Ser Arg Ala
1045 1050 1055

ctg tgg cgg gtg gcc gct gag gag tac gtg gag gtc acg cgg gtg ggg 3216
Leu Trp Arg Val Ala Ala Glu Glu Tyr Val Glu Val Thr Arg Val Gly
1060 1065 1070

gat ttc cac tac gtg acg ggc atg acc act gac aac gta aag tgc cca 3264
Asp Phe His Tyr Val Thr Gly Met Thr Thr Asp Asn Val Lys Cys Pro
1075 1080 1085

tgc cag gtt ccg gct cct gaa ttc ttc acg gag gtg gac gga gtg cgg 3312
Cys Gln Val Pro Ala Pro Glu Phe Phe Thr Glu Val Asp Gly Val Arg
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Leu His Arg Tyr Ala Pro Ala Cys Arg Pro Leu Leu Arg Glu Glu Val
1105 1110 1115 1120

aca ttc cag gtc ggg ctc aac caa tac ctg gtt ggg tca cag cta cca 3408
Thr Phe Gln Val Gly Leu Asn Gln Tyr Leu Val Gly Ser Gln Leu Pro
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tgc gag ccc gaa ccg gat gta gca gtg ctc act tcc atg ctc acc gac      3456
Cys Glu Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr Asp
            1140                1145                1150

ccc tcc cac atc aca gca gaa acg gct aag cgt agg ttg gcc agg ggg      3504
Pro Ser His Ile Thr Ala Glu Thr Ala Lys Arg Arg Leu Ala Arg Gly
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tct ccc ccc tcc ttg gcc agc tct tca gct agc cag ttg tct gcg cct      3552
Ser Pro Pro Ser Leu Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala Pro
    1170                1175                1180

tcc ttg aag gcg aca tgc act acc cac cat gtc tct ccg gac gct gac      3600
Ser Leu Lys Ala Thr Cys Thr Thr His His Val Ser Pro Asp Ala Asp
1185                1190                1195                1200

ctc atc gag gcc aac ctc ctg tgg cgg cag gag atg ggc ggg aac atc      3648
Leu Ile Glu Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Asn Ile
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acc cgc gtg gag tcg gag aac aag gtg gta gtc ctg gac tct ttc gac      3696
Thr Arg Val Glu Ser Glu Asn Lys Val Val Val Leu Asp Ser Phe Asp
            1220                1225                1230

ccg ctt cga gcg gag gag gat gag agg gaa gta tcc gtt ccg gcg gag      3744
Pro Leu Arg Ala Glu Glu Asp Glu Arg Glu Val Ser Val Pro Ala Glu
        1235                1240                1245

atc ctg cgg aaa tcc aag aag ttc ccc gca gcg atg ccc atc tgg gcg      3792
Ile Leu Arg Lys Ser Lys Lys Phe Pro Ala Ala Met Pro Ile Trp Ala
    1250                1255                1260

cgc ccg gat tac aac cct cca ctg tta gag tcc tgg aag gac ccg gac      3840
Arg Pro Asp Tyr Asn Pro Pro Leu Leu Glu Ser Trp Lys Asp Pro Asp
1265                1270                1275                1280

tac gtc cct ccg gtg gtg cac ggg tgc ccg ttg cca cct atc aag gcc      3888
Tyr Val Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Ile Lys Ala
                1285                1290                1295

cct cca ata cca cct cca cgg aga aag agg acg gtt gtc cta aca gag      3936
Pro Pro Ile Pro Pro Pro Arg Arg Lys Arg Thr Val Val Leu Thr Glu
            1300                1305                1310

tcc tcc gtg tct tct gcc tta gcg gag ctc gct act aag acc ttc ggc      3984
Ser Ser Val Ser Ser Ala Leu Ala Glu Leu Ala Thr Lys Thr Phe Gly
        1315                1320                1325

agc tcc gaa tca tcg gcc gtc gac agc ggc acg gcg acc gcc ctt cct      4032
Ser Ser Glu Ser Ser Ala Val Asp Ser Gly Thr Ala Thr Ala Leu Pro
    1330                1335                1340

gac cag gcc tcc gac gac ggt gac aaa gga tcc gac gtt gag tcg tac      4080
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Asp Gln Ala Ser Asp Asp Gly Asp Lys Gly Ser Asp Val Glu Ser Tyr
1345 1350 1355 1360

tcc tcc atg ccc ccc ctt gag ggg gaa ccg ggg gac ccc gat ctc agt 4128
Ser Ser Met Pro Pro Leu Glu Gly Glu Pro Gly Asp Pro Asp Leu Ser
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gac ggg tct tgg tct acc gtg agc gag gaa gct agt gag gat gtc gtc 4176
Asp Gly Ser Trp Ser Thr Val Ser Glu Glu Ala Ser Glu Asp Val Val
1380 1385 1390

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Cys Cys Ser Met Ser Tyr Thr Trp Thr Gly Ala Leu Ile Thr Pro Cys
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1410 1415 1420

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Leu Arg His His Asn Met Val Tyr Ala Thr Thr Ser Arg Ser Ala Gly
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cac tac cgg gac gtg ctc aag gag atg aag gcg aag gcg tcc aca gtt 4416
His Tyr Arg Asp Val Leu Lys Glu Met Lys Ala Lys Ala Ser Thr Val
1460 1465 1470

aag gct aaa ctc cta tcc gta gag gaa gcc tgc aag ctg acg ccc cca 4464
Lys Ala Lys Leu Leu Ser Val Glu Glu Ala Cys Lys Leu Thr Pro Pro
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cat tcg gcc aaa tcc aag ttt ggc tat ggg gca aag gac gtc cgg aac 4512
His Ser Ala Lys Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg Asn
1490 1495 1500

cta tcc agc aag gcc gtt aac cac atc cac tcc gtg tgg aag gac ttg 4560
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Tyr Gly Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Asn
1585                1590                1595                1600

acc tgg aaa tca aag aaa aac ccc atg ggc ttt tca tat gac act cgc      4848
Thr Trp Lys Ser Lys Lys Asn Pro Met Gly Phe Ser Tyr Asp Thr Arg
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tgt ttc gac tca acg gtc acc gag aac gac atc cgt gtt gag gag tca      4896
Cys Phe Asp Ser Thr Val Thr Glu Asn Asp Ile Arg Val Glu Glu Ser
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att tac caa tgt tgt gac ttg gcc ccc gaa gcc aga cag gcc ata aaa      4944
Ile Tyr Gln Cys Cys Asp Leu Ala Pro Glu Ala Arg Gln Ala Ile Lys
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tcg ctc aca gag cgg ctt tat atc ggg ggt cct ctg act aat tca aaa      4992
Ser Leu Thr Glu Arg Leu Tyr Ile Gly Gly Pro Leu Thr Asn Ser Lys
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Gly Gln Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr
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Thr Ser Cys Gly Asn Thr Leu Thr Cys Tyr Leu Lys Ala Ser Ala Ala
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Cys Arg Ala Ala Lys Leu Gln Asp Cys Thr Met Leu Val Asn Gly Asp
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Asp Leu Val Val Ile Cys Glu Ser Ala Gly Thr Gln Glu Asp Ala Ala
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Ser Leu Arg Val Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro
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ggg gac ccg ccc caa cca gaa tac gac ttg gag ctg ata aca tca tgt      5280
Gly Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys
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Ser Ser Asn Val Ser Val Ala His Asp Ala Ser Gly Lys Arg Val Tyr
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Tyr Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu
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Thr Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile Met
        1795                1800                1805

tat gcg ccc act ttg tgg gca agg atg att ctg atg act cac ttc ttc       5472
Tyr Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe
    1810                1815                1820

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Ser Ile Leu Leu Ala Gln Glu Gln Leu Glu Lys Ala Leu Asp Cys Gln
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atc tac ggg gcc tgt tac tcc att gag cca ctt gac cta cct cag atc       5568
Ile Tyr Gly Ala Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro Gln Ile
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Ile Glu Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser
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Pro Gly Glu Ile Asn Arg Val Ala Ser Cys Leu Arg Lys Leu Gly Val
        1875                1880                1885

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cta ctg tcc cag ggg ggg agg gcc gcc act tgt ggc aag tac ctc ttc       5760
Leu Leu Ser Gln Gly Gly Arg Ala Ala Thr Cys Gly Lys Tyr Leu Phe
1905                1910                1915                1920

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Asn Trp Ala Val Lys Thr Lys Leu Lys Leu Thr Pro Ile Pro Ala Ala
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            1940                1945                1950

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        1955                1960                1965

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Arg
1985
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Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys Thr Leu
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Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val Asp Gln
65 70 75 80
Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu Thr Pro
85 90 95
Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala Asp
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Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu Ser
115 120 125
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(71) Applicants (*for all designated States except US*): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI, S.P.A.** [IT/IT]; VIA PONTINA KM. 30.600, I-00040 POMEZIA (IT).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **EMINI, Emilio, A.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **KASLOW, David, C.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **BETT, Andrew, J.** [CA/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **SHIVER, John, W.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **NICOSIA, Alfredo** [IT/IT]; Via Pontina KM. 30.600, I-00040 Pomezia (IT). **LAHM, Armin** [DE/IT]; Via Pontina KM. 30.600, I-00040 Pomezia (IT). **LUZZAGO, Alessandra** [IT/IT]; Via Pontina KM. 30.600, I-00040 Pomezia (IT). **CORTESE, Riccardo** [IT/IT]; Via Pontina KM. 30.600, I-00040 Pomezia (IT). **COLLOCA, Stefano** [IT/IT]; Via Pontina KM. 30.600, I-00040 Pomezia (IT).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

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Published:
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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/031588 A3

(54) Title: HEPATITIS C VIRUS VACCINE

(57) Abstract: The present invention features Ad6 vectors and a nucleic acid encoding a Met-NS3-NS4A-NS4B-NS5A-NS5B polypeptide containing an inactive NS5B RNA-dependent RNA polymerase region. The nucleic acid is particularly useful as a component of an adenovector or DNA plasmid vaccine providing a broad range of antigens for generating an HCV specific cell mediated immune (CMI) response against HCV.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/32512

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/40, 15/51, 15/85, 15/86, 15/861; A61K 48/00
US CL : 514/44; 424/93.2; 435/320.1, 455, 456

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/44; 424/93.2; 435/320.1, 455, 456

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,127,116 A (RICE et al.) 03 October 2000 (03.10.2000), column 45, lines 18-57.	1, 2
A	WO 01/30812 A2 (CHIRON CORPORATION) 03 May 2001 (03.05.2001).	1-54
A	WO 97/47358 A1 (MERCK & CO., INC.) 18 December 1997 (18.12.1997).	1-54

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
09 July 2003 (09.07.2003)

Date of mailing of the international search report
02 SEP 2003

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703)305-3230

Authorized officer
Scott D. Priebe
Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/32512

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-54

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US02/32512

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-54, drawn to a nucleic acid encoding a HCV polyprotein.

Group II, claim(s) 55-59, drawn to a chimeric adenovirus vector comprising sequence derived from human adenovirus serotypes 5 and 6.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature of invention I is a nucleic acid encoding a polyprotein derived from an HCV polyprotein, whereas the technical feature of invention II is a chimeric adenoviral vector comprising a heterologous sequence. These two features are not related. Invention I does not require vector of invention II, nor does is the vector of invention II required to contain the polynucleotides of invention I.

Continuation of B. FIELDS SEARCHED Item 3:

MEDLINE, EMBASE, CAPLUS, BIOSIS, SCISEARCH, USPT, PGPB, DERWENT, GENBANK, GENESEQ
search terms: HCV, hepatitis C virus, vaccine, NS5B, NS5B near inactiv? or non-functional, SEQ ID NO: 1, SEQ ID NO: 2